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FluoMar™, a Fluorous Version of the Marshall Resin for Solution-Phase Library Synthesis

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Abstract

The fluorous counterpart of the Marshall resin, 4-(1*H*,1*H*,2*H*,2*H*-perfluorodecylsulfanyl)phenol (FluoMar™) is prepared by *S*-alkylation of 4-mercaptophenol with C₈F₁₇CH₂CH₂I and employed in the synthesis of amide and diamide analogs. The final products are purified by solid-phase extraction (SPE) over FluoroFlash™ silica cartridges.

Resin-based solid-phase organic synthesis (SPOS) is popular in drug discovery.¹ Its advantage of easy separation, however, is usually counterbalanced by the time-consuming method development, the limitation of reaction scope, and the difficulty of analysis and purification of attached intermediates. Recently Curran and coworkers developed a fluorous tag strategy to overcome some disadvantages associated with the SPOS.² Functionalized perfluoroalkyl groups instead of polymer supports are employed as the “phase tags”.^{2b,3} The separation of fluorous-tagged molecules is carried out over fluorous silica gel based on the strong and selective fluorine-fluorine interaction.⁴

The Marshall resin **1** has been widely used as a carbonate and carbamate linker in solid-phase syntheses.⁵ The linker can be cleaved with primary and secondary amines to afford the corresponding amides either directly or after oxidation of the sulfide to the sulfone.⁶ Described in this paper is the synthesis of fluorous version of Marshall resin, perfluoroalkylsulfanylphenol **2** (FluoMar™). The utility of this compound is illustrated by the solution-phase synthesis of amides and diamides.

The FluoMar™ **2** was readily prepared by *S*-alkylation of 4-mercaptophenol with C₈F₁₇CH₂CH₂I and purified by flash column chromatography on normal silica gel (Scheme 1).^{7,8} The ethylene spacer between the C₈F₁₇ tag and the sulfur is expected to minimize the strong electron-withdrawing effect from the perfluoroalkyl group and maintain the nucleophilicity of the hydroxy group. This compound has the general features of organic

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molecules; it dissolves well in common solvents such as CH₂Cl₂, THF, and AcOEt, and can be analyzed by traditional chromatographic and spectroscopic methods.

With compound **2** in hand, we first validated the attachment to carboxylic acids **3** and the tag cleavage by the amine displacement (Scheme 2). The coupling of **2** with indole-5-carboxylic acid **3****{1}** (2.0 equiv) or 7-methoxy-2-benzofurancarboxylic acid **3****{2}** was carried out under a standard solution-phase conditions with 2.0 equiv of diisopropylcarbodiimide (DIC) and 1.0 equiv of dimethylaminopyridine (DMAP) in DMF. These intermediates were purified by regular flash column chromatography. Compounds **4****{1}** and **4****{2}** were each split to three portions and directly displaced with three primary amines **5****{1-3}** without oxidation of the sulfur to give the corresponding amides **6****{1-2,1-3}**. After a quick acidic workup with 1.0 N HCl to remove the unreacted amine,⁹ the crude product was loaded onto a FluoMarTM cartridge and the MeOH/H₂O fraction was collected to give analytically pure product. The FluoMarTM tag **2** was recovered in the MeOH fraction in 65–70% yield.

Encouraged by the preliminary results, we next explored the use of FluoMarTM **2** in a multi-step parallel synthesis of diamides (Scheme 3). The N-Boc isonipecotic acid **7** was coupled with **2** followed by deprotection with TFA and N-acylation with three different acid halides. The resulting compounds **9****{1-3}** were each split into three portions and displaced by three amines resulting in a demonstration library of diamides **10****{1-3,1-3}**.¹¹ The final products were purified by SPE and cleaved FluoMarTM **2** was recovered in an average yield of 65%. Figure 1 shows a typical ¹H NMR trace of the products prior and after SPE; the crude mixture containing **10****{1,2}** and cleaved tag **2** (top trace of Figure 1), the MeOH/H₂O fraction containing **10****{1,2}** (middle trace of Figure 1), and the MeOH fraction containing recovered FluoMar **2** (bottom trace of Figure 1).

We also carried out a simple experiment to estimate the reactivity difference between the Marshall resin **1** and FluoMarTM **2** towards a typical carboxylic acid. Equimolar amounts of **1**¹² and **2** (1.0 equiv each) were mixed with 1.0 equiv of benzofuran carboxylic acid under a standard coupling condition used in the synthesis of amide **4** and diamides **8** (Scheme 4). The reaction was stopped after 8 h when all the acid was consumed as indicated by TLC analysis. The resin was filtered off from the reaction mixture and washed with DMF and CH₂Cl₂. The filtrate was analyzed by the HPLC and the ratio of product **11** to the unreacted **2** was 73:27 with the assumption that the 27% unreacted FluoMarTM **2** was due to a competitive reaction of the acid **3** with the Marshall resin. This result suggested that despite the electron withdrawing effect of the fluororous chain, fluororous tag still reacted as least 2.7 times faster than the resin.

recyclable phase tag in the solution-phase synthesis of amides and diamides. This reagent can be used as an alternative to the Marshall resin in combinatorial and parallel synthesis.

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12. Purchased from Aldrich, loading 1.0–1.5 mmol/g, polystyrene with 1% cross linking with DVB. An average loading of 1.25 mmol/g was used for the calculation.

Top trace: crude product containing **10{1,2}** and **2**. Middle trace: product **10{1,2}**. Bottom trace: recovered tag **2**

Figure 1.
 ^1H NMR spectra of product **10{1,2}** and recovered **2**

Scheme 1.
Preparation of FluoMar™

Scheme 2.
Synthesis of 2x3 array of amides **6**{ R^1, R^2 }

	1	2	3
R ¹	Cl	H	OMe
R ²	nBu—
	10 {1,1}, 93%	10 {2,1}, 90%	10 {3,1}, 90%
	10 {1,2}, 100%	10 {2,2}, 95%	10 {3,2}, 100%
	10 {1,3}, 37%	10 {2,3}, 21%	10 {3,3}, 55%

i. 1.0 equiv of **2**, 2.0 equiv of **7**, 2.0 equiv DIC, 1.0 equiv DMAP, DMF, 25 °C, 8 h, SPE, 71%. ii. 9.0 equiv TFA, CH₂Cl₂, 25 °C, 8 h, SPE, 100%. iii. 1.5 equiv R¹PhCO₂Cl, 1.5 equiv Et₃N, THF, 55 °C, SPE, 73-78%. iv. 1.5 equiv R²NH₂, THF, 60 °C, 5 h, SPE, 21-100%

Scheme 3.
Synthesis of 3x3 array of diamides **10**{R^I, R²}

i. 1.0 equiv **1**, 1.0 equiv **2**, 1.0 equiv **3**, 2.0 equiv DIC,
1.0 equiv DMAP, DMF, 25 °C, 8 h

Scheme 4.

Competitive tagging of **3** with Marshall resin **1** and FluoMar™ **2**