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

Christine Hiu-Tung Chen and Wei Zhang*

Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, Pennsylvania 15238

w.zhang@fluorous.com

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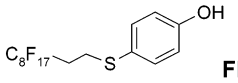
ABSTRACT

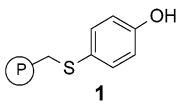


FluoMar™

The fluorous counterpart of the Marshall resin, 4-(*1H,1H,2H,2H*-perfluorodecylsulfanyl)phenol (FluoMar), is prepared by *S*-alkylation of 4-mercaptophenol with $C_8F_{17}CH_2CH_2I$ and employed in the synthesis of amide and diamide analogues. The final products are purified by solid-phase extraction (SPE) over Fluoro*Flash* silica cartridges.

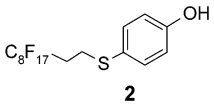
Resin-based solid-phase organic synthesis (SPOS) is popular in drug discovery.[1] Its advantage of easy separation, however, is usually counterbalanced by the time-consuming method of development, the limitation of reaction scope, and the difficulty of analysis and purification of attached intermediates. Recently Curran and co-workers 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 the fluorous version of the Marshall resin, perfluoroalkylsulfanylphenol **2** (FluoMar). The utility of this compound is illustrated by the solution-phase synthesis of amides and diamides.



1

Marshall Resin

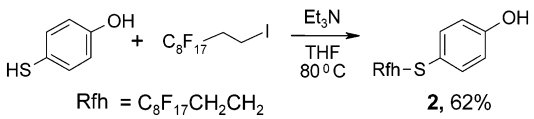


2

FluoMar™

FluoMar **2** was readily prepared by *S*-alkylation of 4-mercaptophenol with $C_8F_{17}CH_2CH_2I$ and purified by flash column chromatography on normal silica gel (Scheme 1).[7,8]

Scheme 1. Preparation of FluoMar **2**



Rfh = $C_8F_{17}CH_2CH_2$ **2**, 62%

The ethylene spacer between the C_8F_{17} tag and the sulfur is expected to minimize the strong electron-withdrawing effect

(1) Reviews: (a) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091. (b) Dorwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, Germany, 2000. (c) Burgess, K. *Solid*-Phase Organic Synthesis; John Wiley & Sons: New York, 2000. (d) *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Vols. 1 and 2.

(2) (a) Curran, D. P. *Chemtracts-Org. Chem.* **1996**, *9*, 75. (b) Curran, D. P. *Angew.* Chem., *Int. Ed.* **1998**, *37*, 1175. (c) Curran, D. P. In *Stimulating Concepts in Chemistry*; Stoddard, F., Reinhoudt, D., Shibasaki, M., Eds.; Wiley-VCH: New York, 2000; p 25. (d) Curran, D. P.; Hadida, S.; Studer, A.; He, M.; Kim, S.-Y.; Luo, Z.; Larhed, M.; Hallberg, M.; Linclau, B. In *Combinatorial Chemistry*: *A Practical Approach*; Fenniri, H., Ed.; Oxford University Press: Oxford, UK, 2001; Vol. 2, p 327.

(3) (a) Yoshida, J.-I.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693. (b) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964.

(4) Curran, D. P. *Synlett* **2001**, 1488.

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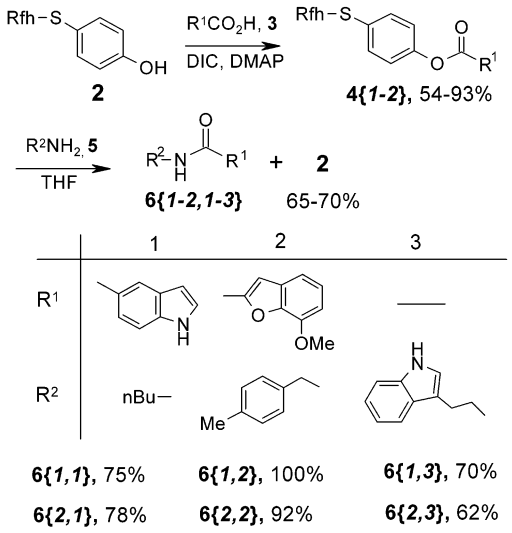
from the perfluoroalkyl group and maintain the nucleophilicity of the hydroxy group. This compound has the general features of organic molecules: it dissolves well in common solvents such as CH_2Cl_2, THF, and AcOEt, and can be analyzed by traditional chromatographic and spectroscopic methods.

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-

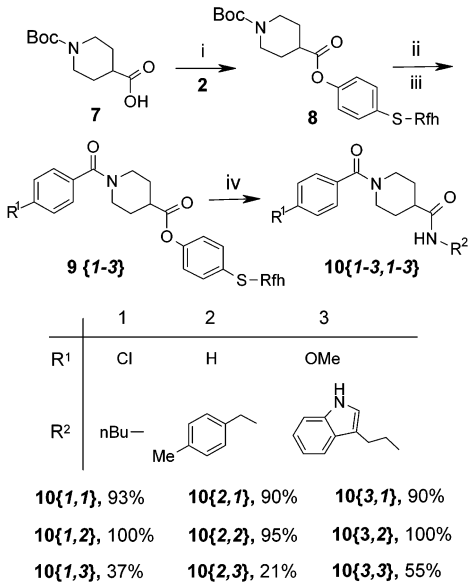
Scheme 2. Synthesis of a 2 × 3 Array of Amides **6**{***R*^{1},***R*^{2}}



carboxylic acid **3**{***1***} (2.0 equiv) or 7-methoxy-2-benzofurancarboxylic acid **3**{***2***} was carried out under standard solution-phase conditions with 2.0 equiv of diisopropylcarbodiimide (DIC) and 1.0 equiv of (dimethylamino)pyridine (DMAP) in DMF. This intermediate was 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 Fluoro*Flash* cartridge and the MeOH/H_2O fraction was collected to give analytically pure product. The FluoMar tag **2** was recovered in the MeOH fraction in 65−70% yield.

Encouraged by the preliminary results, we next explored the use of FluoMar **2** in a multistep parallel synthesis of diamides (Scheme 3). The *N*-Boc isonipecotic acid **7** was

Scheme 3. Synthesis of a 3 × 3 Array of Diamides **10**{***R*^{1},***R*^{2}}[a]



[a] Reagents and conditions: (i) 1.0 equiv of **2**, 2.0 equiv of **7**, 2.0 equiv of DIC, 1.0 equiv of DMAP, DMF, 25 °C, 8 h, SPE, 71%. (ii) 9.0 equiv of TFA, CH_2Cl_2, 25 °C, 8 h, SPE, 100%. (iii) 1.5 equiv of R^1PhCO_2Cl, 1.5 equiv of Et_3N, THF, 55 °C, SPE, 73-78%. (iv) 1.5 equiv of R^2NH_2, THF, 60 °C, 5 h, SPE, 21−100%.

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 FluoMar **2** was recovered in an average yield of 65%. Figure 1 shows a typical ^{1}H NMR trace of the products prior to and after SPE: the crude mixture containing **10**{***1,2***} and cleaved tag **2** (top trace of Figure 1), the MeOH/H_2O 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

(5) Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867.

(6) (a) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097. (b) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295. (c) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron* **1998**, *39*, 1291. (d) Dressman, B.; Singh, U.; Kaldor, S. W. *Tetrahedron Lett.* **1998**, *39*, 3631. (e) Breitenbucher, J. G.; Hui, H. C. *Tetrahedron Lett.* **1998**, *39*, 8207. (f) Yan, B.; Nguyen, N.; Liu, L.; Holland, G.; Raju, B. *J. Comb. Chem.* **2000**, *2*, 66. (g) Beech, C.; Coope, J.; Fairley, G.; Gilgert, P.; Main, B.; Ple, K. *J. Org. Chem.* **2001**, *66*, 2240. (h) Fang, L.; Demee, M.; Sierra, T.; Kshirsagar, T.; Celebi, A. A.; Yan, B. *J. Comb. Chem.* **2002**, *4*, 362.

(7) Selective *S*-alkylation of 4-mercaptophenol, see: Breitenbucher, J. G.; Johnson C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett*. **1998**, *39*, 1295.

(8) Perfluoroalkylsulfanylphenol **2** has been used as a photoimaging compound, see: Wakamatsu, K.; Wakata, Y.; Satomura, M.; Namiki, T. European Patent 468531 A1, 1992.

(9) Our recent study and an independent work from Lindsley (ref 10) demonstrated that amines could be retained on the SPE cartridge by adding acidic ion-exchange resin on top of the fluorous silica. No more acidic workup was needed prior to the SPE.

(10) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Strauss K. A. *Tetrahedron Lett*. **2002**, *43*, 6319.

(11) A general protocol for the synthesis of diamide **10** from **9**. FluoMar-bound intermediate **9** (0.127 mmol) was dissolved in THF (1.0 mL) in a capped vial. The amine (1.2 equiv) was added and the reaction mixture was stirred at 60 °C for 5 h. An aqueous solution of 1.0 N HCl (1.0 mL) was added and the vial was shaken with 0.5 mL of EtOAc. The EtOAc layer was loaded onto a 2 g Fluoro*Flash* cartridge and eluted with MeOH/H_2O (80/20). The first 8-mL fraction contained the desired product and the subsequent fraction eluted with MeOH contained the displaced fluorous tag.

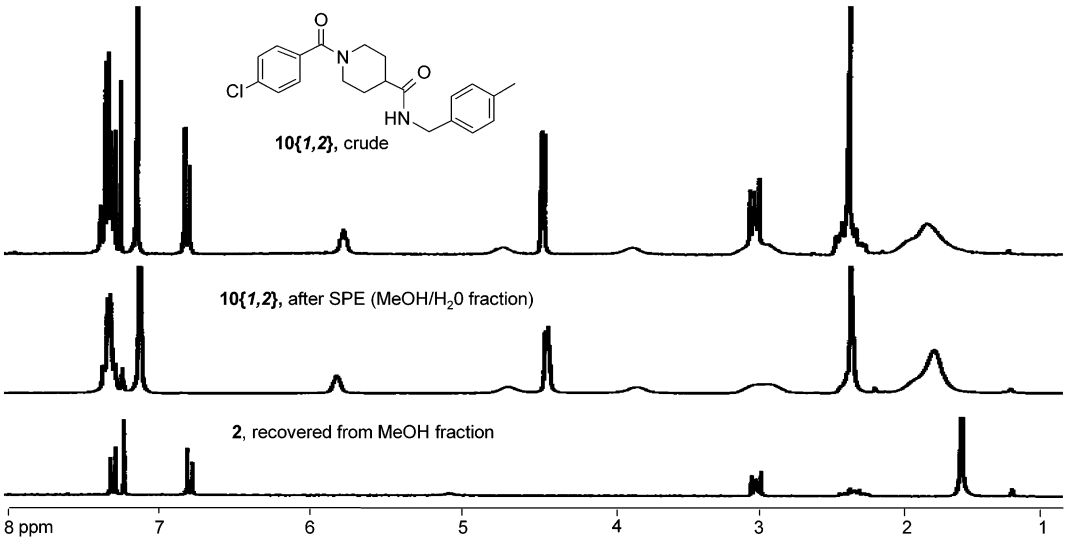
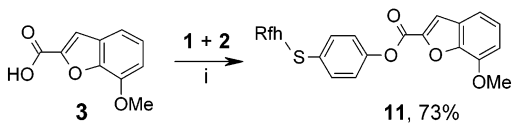


Figure 1. ^{1}H NMR spectra of product **10**{***1,2***} and recovered **2**. Top trace: crude product containing **10**{***1,2***} and **2**. Middle trace: product **10**{***1,2***}. Bottom trace: recovered tag **2**.

FluoMar **2** toward 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 CH_2Cl_2. The filtrate was analyzed by HPLC and the ratio of product **11** to the unreacted **2** was 73:27 with the assumption that the 27% unreacted FluoMar **2** was due to a competitive reaction of acid **3** with the Marshall resin. This result suggested that despite the electron-withdrawing effect of the fluorous chain, FluoMar still reacted as least 2.7 times faster than the resin.

Scheme 4. Competitive Tagging of **3** with Marshall Resin **1** and FluoMar **2**[a]



[a] Reagents and conditions: (i) 1.0 equiv of **1**, 1.0 equiv of **2**, 1.0 equiv of **3**, 2.0 equiv of DIC, 1.0 equiv of DMAP, DMF, 25 °C, 8 h.

In summary, we have employed FluMar **2** as a 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.