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Fluorous Synthesis of Disubstituted Pyrimidines

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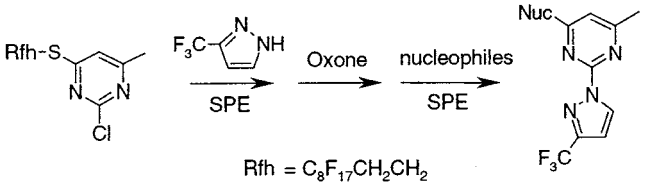
ABSTRACT



The fluorous synthesis of disubstituted pyrimidines is carried out by attaching 2,4-dichloro-6-methylpyrimidine with 1*H*,1*H*,2*H*,2*H*-perfluorodecanethiol. The tagged substrate is substituted with 3-(trifluoromethyl)pyrazole followed by thioether oxidation and tag displacement with amines or thiols. The fluorous chain serves as a phase tag for intermediate and product purification over Fluoro*Flash* SPE cartridges.

Because of their important biological activities, substituted *N*-heterocycles such as pyrimidines, quinazolines, and purines, are the targets of many solid-phase syntheses.[1] The large majority of these reactions are based on the nucleophilic substitution of halogenated *N*-heterocycles attached to nitrogen- or sulfur-based linkers. The sulfur linker is popular because it can be activated by oxidation and displaced by a wide variety of nucleophiles to introduce new diversity into the molecule.[2]

Recently, fluorous technologies have been developed as solution-phase alternatives for high-throughput organic synthesis.[3,4] Functionalized perfluoroalkyl chains, instead of polymers, are used as phase tags attached to substrates or reagents for fluorous synthesis. Fluorous mixture synthesis[5] and parallel synthesis using fluorous reagents,[6] scavengers,[7,8] and protecting groups[5,9] have previously been reported. Described in this paper is a fluorous catch and release technique for the synthesis of disubstituted pyrimidines.

Fluorous thiols are good nucleophiles that have been used as scavengers for halides in parallel synthesis of a secondary

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(8) Fluorous quenching combined with liquid−liquid extraction, see: (a) Curran, D. P.; Hadida, S.; Kim, S. Y.; Luo, Z. Y. *J. Am. Chem. Soc.* **1999**, *121*, 6607. (b) Linclau, B.; Singh, A. K.; Curran, D. P. *J. Org. Chem*. **1999**, *64*, 2835. (c) Wipf, P.; Reeves, J. T.; Balachandran, R.; Giuliano, K. A.; Hamel, E.; Day, B. W. *J. Am. Chem. Soc.* **2000**, *122*, 9391.

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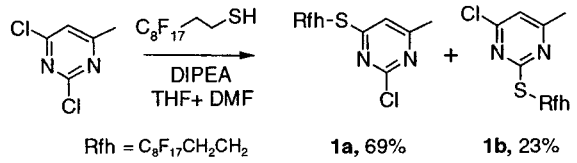
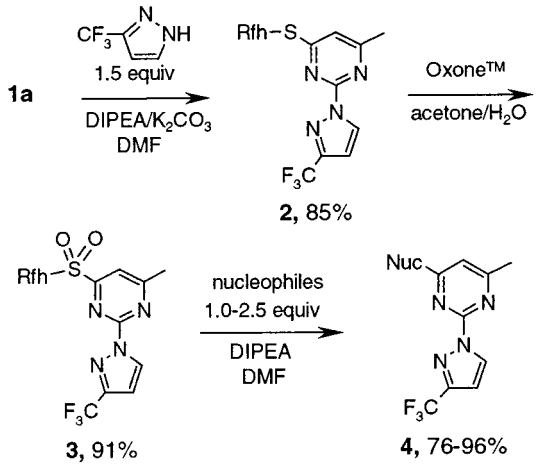
amine library.[7a] To demonstrate its utility as a phase tag in fluorous synthesis, a fluorous thiol 1*H*,1*H*,2*H*,2*H*-perfluorodecanethiol was attached to the electron-deficient 2,4-dichloro-6-methylpyrimidine by a nucleophilic substitution in the presence of diisopropylethylamine (DIPEA) (Scheme 1).[10] Two regioisomers **1a** and **1b** were generated in a ratio

Scheme 1



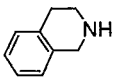
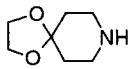
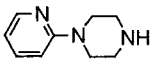
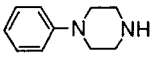
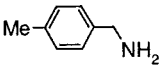
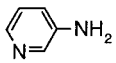
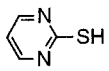
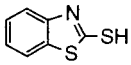
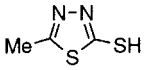
of 3:1 by HPLC analysis. If polymeric tags were used, regioisomers such as **1a** and **1b** could not be separated. However, fluorous compounds **1a** and **1b** were readily separated by flash column chromatography on normal silica gel on the basis of their different polarity. The major isomer **1a** was used for further nucleophilic substitution with 3-(trifluoromethyl)-pyrazole to give **2** (Scheme 2).[11] The

Scheme 2



fluorous sulfur tag was then activated by oxidation with Oxone followed by the displacement with 10 assorted nucleophiles, including primary and secondary amines and thiols to yield disubstituted pyrimidines **4** (Table 1).[12,13] Results were excellent: yields of **4a**−**j** ranged from 74 to 96%, and purities were usually above 90%.

Table 1. Structures, Yields, and Purities of Disubstituted Pyrimidines **4a**−**j**

entry	nucleophile	equiv	product	yield (purity)[a]
1		2.5	**4a**	96% (97%)
2		2.0	**4b**	91% (93%)
3		2.0	**4c**	82% (92%)
4		2.5	**4d**	93% (90%)
5		2.5	**4e**	79% (90%)
6		1.2	**4f**	88% (89%)
7		1.2	**4g**	74% (93%)
8		1.0	**4h**	76% (97%)
9		1.0	**4i**	84% (92%)
10		1.0	**4j**	77% (90%)

[a] Purity was assessed by HPLC on a C18 column with a UV detector at 254 nm.

An important feature of fluorous synthesis is the employment of simple solid-phase extraction (SPE) over Fluoro*Flash* cartridges charged with fluorous silica gel that has a perfluorocarbon bonded-phase to selectively retain fluorous molecules while organic compounds pass through as fast as the solvent front.[4,14] Only two fractions need to be collected from the SPE: an 80/20 MeOH/H_2O fraction containing nonfluorous compounds and a MeOH fraction containing fluorous compounds. The strong fluorine−fluorine interaction

(10) Synthesis of **1a**. To a solution of 2,4-dichloro-6-methylpyrimidine (2.1 g, 12.9 mmol) and fluorous thiol (6.1 g, 12.9 mmol) in DMF (50 mL) was added DIPEA (4.5 mL, 25.8 mmol). After stirring at room temperature for 1 h, the reaction mixture was mixed with H_2O and extracted with EtOAc. The organic layer was washed with aqueous NH_4Cl, dried over $MgSO_4$, and concentrated. HPLC analysis of the crude product indicated **1a** and **1b** in a ratio of 3:1. The desired product **1a** (5.4 g, 69% yield) was isolated using flash column chromatography on silica gel with 90/10 hex/EtOAc. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H), 2.63 (m, 2H), 3.42 (m, 2H), 6.98 (s, 1H). MS *m*/*z* (rel intensity): 606 (M^+, 23), 368 (11), 236 (6), 187 (100).

(11) Synthesis of **2**. To a solution of **1a** (0.50 g, 0.82 mmol) and 3-trifluoromethylpyrazole (0.17 g, 1.25 mmol) in DMF (40 mL) were added DIPEA (217 μL, 1.25 mmol) and K_2CO_3 (113 mg, 0.82 mmol). After heating at 80 °C for 12 h, the reaction mixture was extracted with EtOAc, washed with aqueous NH_4Cl, dried over $MgSO_4$, and concentrated. The crude product was purified by SPE on a 5 g Fluoro*Flash* cartridge eluted with 80/20 MeOH/H_2O (20 mL) and then MeOH (20 mL). The MeOH fraction was concentrated to give **2** (0.49 g, 85%). ^1H NMR ($CDCl_3$): δ 2.57 (s, 3H), 2.74 (m, 2H), 3.47 (m, 2H), 6.74 (d, 1H), 7.23 (s, 1H), 8.58 (br s, 1H). MS *m*/*z* (rel intensity): 706 (M^+, 30), 687 (9), 631 (10), 287 (100).

(12) Synthesis of **3**. To a solution of **2** (100 mg, 0.14 mmol) in acetone (10 mL) was added a solution of Oxone (350 mg, 0.56 mmol) in H_2O (3 mL) at room temperature. After heating at 60 °C for 12 h, a white precipitate was filtered from the reaction mixture. The filtrate was extracted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated to give **3** (94 mg, 91%). This compound was used in the next reaction step without further purification. ^1H NMR ($CDCl_3$): δ 2.83 (s, 3H), 2.93 (m, 2H), 3.75 (m, 2H), 6.81 (d, 1H), 7.81 (s, 1H), 8.66 (br s, 1H). MS *m*/*z* (rel intensity): 739 ($M^+ + 1$, 100).

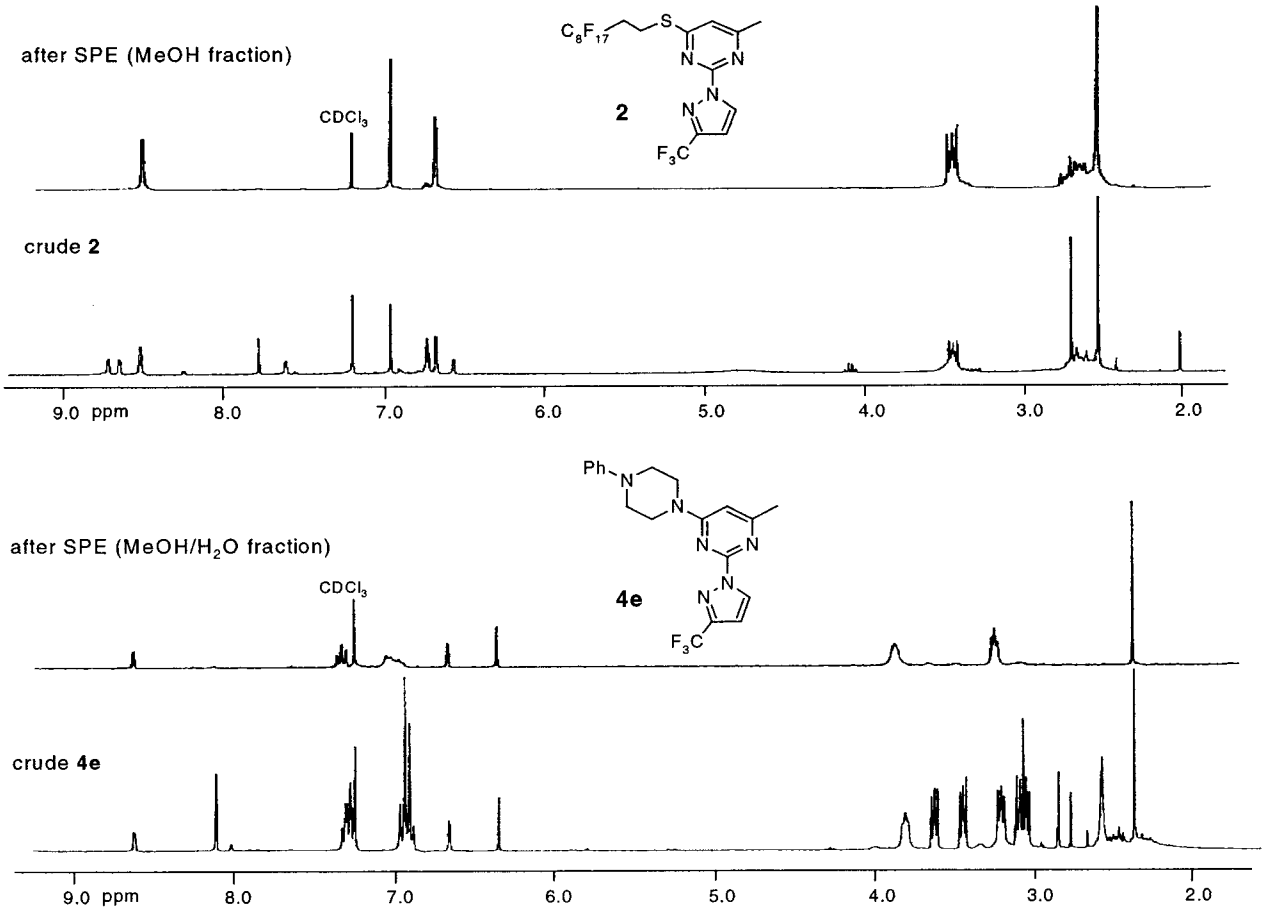


Figure 1. ^{1}H NMR spectra of intermediate **2** and product **4e** before and after SPE.

retains small molecules tagged with a light fluorous ponytail (C_8F_{17}) on fluorous silica gel until elution with a stronger solvent such as MeOH. Fluorous intermediate **2** was purified by SPE and collected from the MeOH fraction, while product **4** was collected from the MeOH/H_2O fraction. The DIPEA used for the reaction of **1a** can be removed by acidic workup prior to SPE. The crude product containing the cleaved tag, DIPEA, and excess nucleophile was purified by loading onto a Fluoro*Flash* cartridge with a small amount of weak acidic ion-exchange resin (Amberlite CG-50) on top of the fluorous silica and eluted with 80/20 MeOH/H_2O. The cleaved tag was retained by the fluorous silica, and amines were retained by the ionic exchange resin.[7c] We found that the CF_3 group of products **4** did not hold the molecules against elution with MeOH/H_2O. Most products had purities greater than 90% after SPE. The ^{1}H NMR spectra of intermediate **2** and product **4e** demonstrate the efficiency of SPE (Figure 1). The crude intermediate **2** was separated from the excess 3-(trifluoromethyl)pyrazole by collecting the MeOH fraction. The crude product **4e** containing excess 4-phenylpiperazine, DIPEA, and cleaved fluorous tag was purified by collecting the MeOH/H_2O fraction from a cartridge charged with fluorous silica and acidic ion-exchange resin.

Synthesis of substituted pyrimidines exemplifies the unique character of fluorous synthesis, including the use of tag strategy for quick SPE, analysis and separation of tagged isomers by conventional tools, and adaptability of traditional solution-phase reaction conditions. The "beadless" and traceless fluorous thiol tag is complementary to corresponding thiol linkers in solid-phase synthesis. The catch and release method with the fluorous thiol can be applied to the synthesis of other substituted *N*-heterocyles.

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(13) Synthesis of **4a** as a representative protocol. To a solution of **3** (15 mg, 0.02 mmol) in DMF (0.5 mL) were added morpholine (5 mg, 0.05 mmol) and DIPEA (3.5 μL, 0.02 mmol). After being heated at 80 °C for 10 h, the reaction mixture was loaded onto a 2 g Fluoro*Flash* cartridge containing 100 mg of exchange resin (Amberlite CG-50) on top of the fluorous silica and eluted with 80/20 MeOH/H_2O (10 mL) and then with MeOH (10 mL). The MeOH/H_2O fraction was concentrated to give **4a** (6 mg, 96%). ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H), 3.72 (br m, 4H), 3.83 (m, 4H), 6.33 (s, 1H), 6.69 (d, 1H), 8.61 (br s, 1H). MS *m*/*z* (rel intensity): 314 ($M^+ + 1$, 100).

(14) Fluoro*Flash* SPE cartridges are available from Fluorous Technologies, Inc., via the Internet at www.fluorous.com.