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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 *1H,1H,2H,2H*-perfluorodecanethiol. The tagged substrate is substituted with 3-(trifluoromethyl)pyrazole followed by thioether oxidation and tag displacement with amines and thiols. The fluorous ponytail 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 to the molecule.[2]

Recently, fluorous technologies have been developed as solution-phase alternatives for high-throughput synthesis.[3] Functionalized perfluoroalkyl groups, instead of polymers, are used as phase tags attached to substrates or reagents for fluorous synthesis.[4] Fluorous mixture synthesis[5] and parallel synthesis using fluorous reagents[6], scavengers[7], and protecting groups[5,8] 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 amine library.[7a] To demonstrate its utility as a phase tag in fluorous synthesis, a fluorous thiol *1H,1H,2H,2H*-perfluorodecanethiol was attached to the electron deficient 2,4-dichloro-6-methylpyrimidine by a nucleophilic substitution (Scheme 1).

Two regioisomers **1a** and **1b** were generated in a ratio of 3:1 by HPLC analysis. If polymeric tags were used, regioisomers like **1a** and **1b** would not be separated. However, fluorous compounds **1a** and **1b** were readily separated by flash column chromatography on normal silica gel based on their different polarity. The major isomer **1a** was used for further nucleophilic substitution with 3-(trifluoromethyl)pyrazole to give **2** (Scheme 2). The fluorous sulfur tag was then activated by oxidation with Oxone™ followed by the displacement with ten assorted nucleophiles including primary and secondary amines and thiols to yield disubstituted pyrimidines **4** (Table 1).

An important feature of fluorous synthesis is the employment of simple solid-phase extraction (SPE) over Fluoro*Flash*™ cartridges charged with fluorous silica.[4,9] Only two fractions need to be collected from the SPE; a MeOH/H_2O (80/20) fraction containing non-fluorous compounds and a MeOH fraction containing fluorous compounds. The strong fluorine-fluorine interaction retains small molecules tagged with a light fluorous ponytail (C_8F_{17}) on fluorous

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silica gel until elution with a stronger solvent such as MeOH. Fluorous intermediates **2** and **3** were purified by SPE and collected in the MeOH fraction, while product **4** was collected in the MeOH/H_2O fraction. Because diisopropylethylamine (DIPEA) and excess nucleophiles were used for the last reaction step, a small amount of weak acidic ion exchange resin (Amberlite™ CG-50) was placed on top of the fluorous silica for the retention of both the cleaved fluorous tag and amines.[7c] We found that CF_3 group of products **4** did not hold the molecules against elution with MeOH/H_2O. All products had purities greater than 90% after SPE. The ^1H 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 characters 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 and supplementary to corresponding thiol linkers in solid-phase synthesis. The catch and release method with the fluorous thiol has good potential in the synthesis of other substituted N-heterocyles.

Acknowledgements

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References and notes

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9. Fluorous thiol and Fluoro*Flash*™ SPE cartridges are available from Fluorous Technologies, Inc. www.fluorous.com

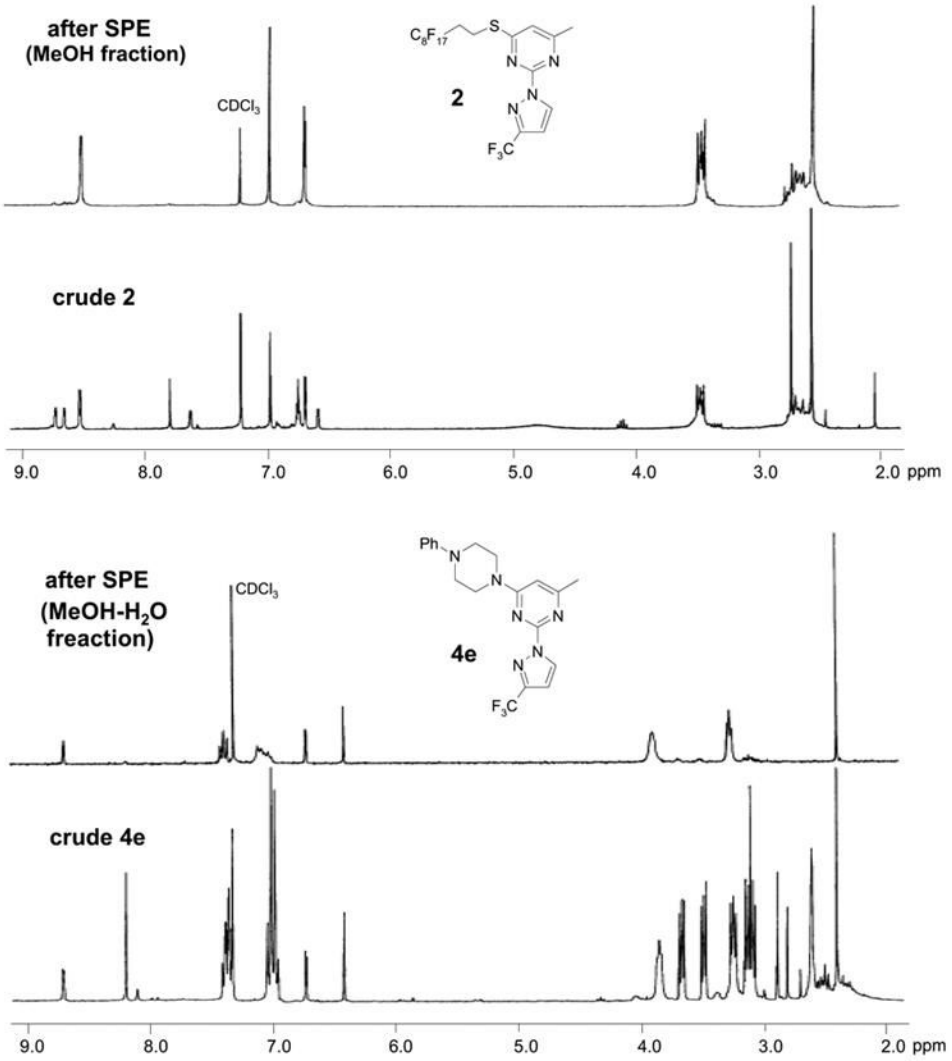
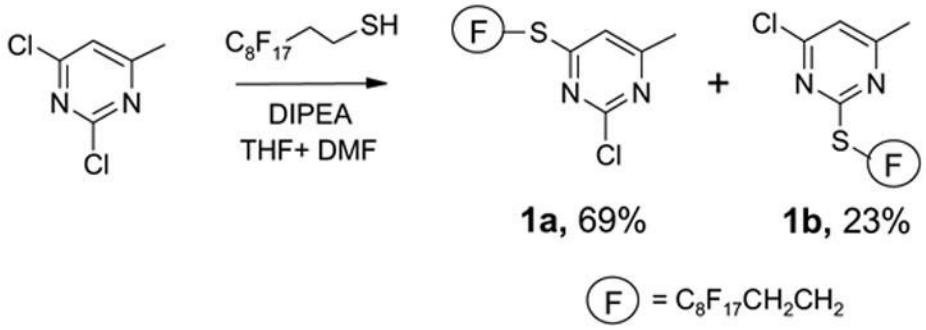
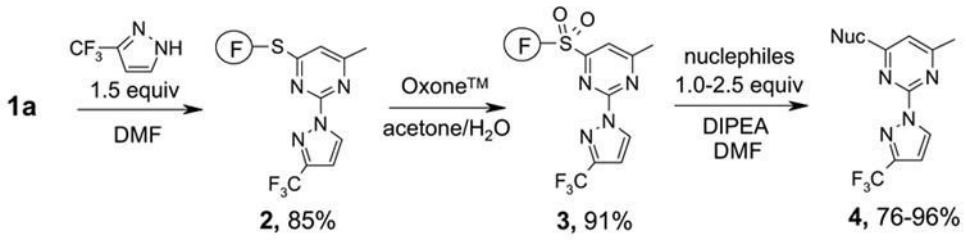


Figure 1.
^{1}H NMR spectra of intermediate 2 and product 4e before and after SPE



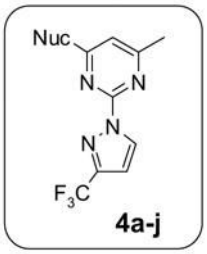
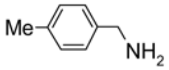
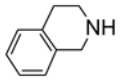
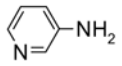
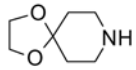
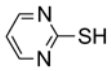
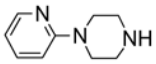
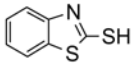
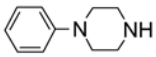
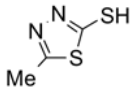
Scheme 1.



Scheme 2.

Table 1

Structures, yields, and purities of disubstituted pyrimidines

		nucleophile	equiv	yield (purity) [a]		nucleophile	equiv	yield (purity)
	**a**		2.0	96% (97%)	**f**		1.5	88% (89%)
	b		2.0	91% (93%)	**g**		1.5	74% (93%)
	c		2.0	82% (92%)	**h**		1.0	76% (97%)
	d		2.5	93% (90%)	**i**		1.0	84% (92%)
	e		2.5	79% (90%)	**j**		1.0	77% (90%)

[a] purity was assessed by ^{1}H NMR and HPLC on a C18 column with a UV 254nm detector