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Traceless Linker: Oxidative Activation and Displacement of a Sulfur-Based Linker

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Abstract. The construction of small heterocycles using solid-phase chemistry is usually done through the use of a polar group to attach the compounds to the resin. These polar functionalities invariably become part of the structure and eventually limit the structure-activity relationships derived from these compounds. We have identified a method for overcoming some of these limitations. A sulfur-based linker has been identified that can serve not only as a point of attachment for a small heterocycle, but also as a means to introduce further diversity into the molecule. The linker remains inert until "activated" by oxidation. A limiting amount of a nucleophile can then be used to cleave the molecule from the resin and introduce additional diversity into the molecule.

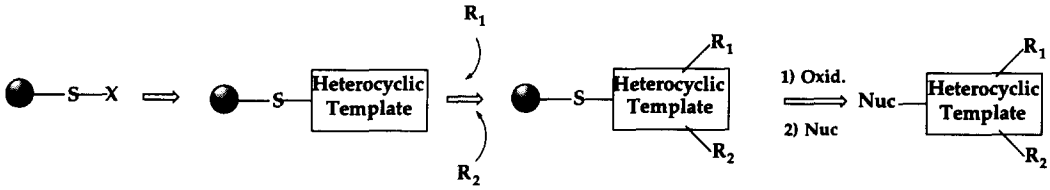
Combinatorial chemistry and parallel synthesis techniques are gaining wide acceptance as methods for generating new leads and for optimizing hits identified from high throughput screens. Solid-phase approaches have been used most widely in the generation of libraries for lead discovery. However, the use of solid-phase approaches can be detrimental to the lead optimization process, since the compounds are attached to the solid-phase resin through a polar functionality (i.e. OH, NH_2, COOH). Therefore, this attachment point invariably becomes part of the structure and thus the structure-activity relationships and may limit the utility of these techniques for optimizing leads. Several groups have recently reported methods for overcoming these limitations through the use of traceless linkers. These include the use of activatable linkers,[1] photolabile linkers,[2] and silicon linkers. [3]

As part of our ongoing studies aimed toward the identification of new techniques for combinatorial chemistry and its applications to lead optimization, we have been examining new traceless linker methodologies. As outlined in Figure 1, our strategy involves the use of an activatable sulfur linkage. The goal is to attach compounds or build heterocycles on a solid phase via a sulfur linkage that would remain inert throughout the synthesis. Upon oxidation to the sulfone, this linker becomes "activated" and hopefully can be displaced by a wide variety of nucleophiles. This activatable, traceless linker would allow for the

introduction of additional diversity into the structures (cleavage-diversification).[1] If successful, this approach would provide access to a variety of highly substituted heterocycles previously not available, or provide methodology for modifying existing templates more effectively.

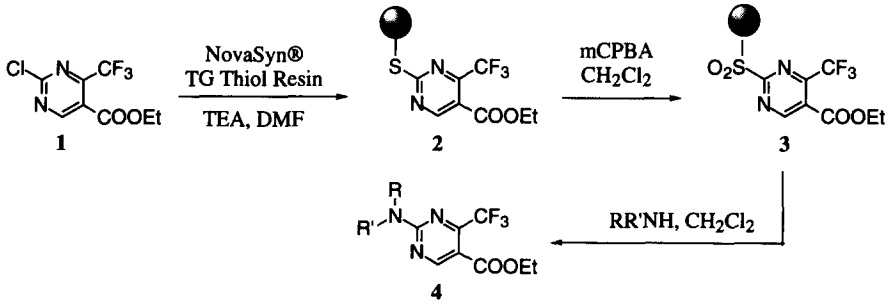
Prior to embarking on a full program of new library synthesis, we thought it critical to answer two key questions: 1) if the sulfur linkage can be activated and displaced ("cleaved") from the resin with a limiting amount of reagent (to eliminate excess purification) and 2) if the linker will be stable to a variety of reaction conditions that are commonly performed on a solid phase. Herein, we report our preliminary studies.

Figure 1



To begin our model studies, we attached commercially available 2-chloro-4-trifluoromethyl pyrimidine-5-carboxylate **1** to the thio PEG resin[4] to provide **2** (Scheme 1). Treatment of **2** with an excess of mCPBA in dichloromethane provided the sulfone **3**. Initially, compound **3** was treated with an excess of n-butylamine to provide compound **4** (R' = n-butyl, R = H, determined by NMR) thus proving that the group can serve as a traceless linker (reaction of **2** with n-butylamine resulted in no reaction).

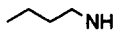
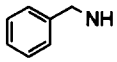
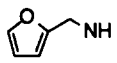
Scheme 1



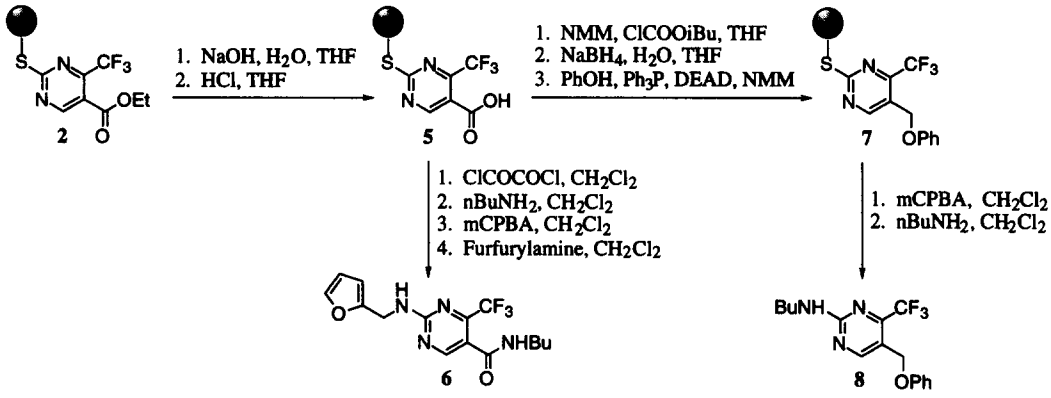
To determine the utility of this methodology, we treated compound **3** with a variety of amines and anilines as shown in Table 1. A limiting amount of each nucleophile was used to ensure that only the desired product was obtained (cleaved) and that no purification would be required (no excess reagents). All of the nucleophiles reacted at the desired position resulting in the release of the final product cleanly from the resin (as indicated by GC/MS, HPLC).

For this process to be useful, the linker must be stable to a number of reaction conditions. Therefore, compound **2** was subjected to a variety of conditions including saponification, conversion to the acid chloride, reduction to the alcohol, and Mitsunobu conditions. The compounds were again activated with mCPBA, and an amine used to introduce another functionality and release the compound cleanly from the resin (Scheme 2).[5]

TABLE 1

Compound	2-Substituent	Overall Yield (%)	Purity (%)
4a	NH_2	87	94
4b		93	96
4c		90	90
4d		50	50
4e		88	95
4f		80	92

SCHEME 2



In summary, we have demonstrated the stability of this linker for modifying compounds attached to a resin and its use for the introduction of additional diversity onto small heterocycles. We are now embarking on a program to prepare small heterocycle-based libraries that can be constructed on a solid-phase using this chemistry.[6]

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REFERENCES AND NOTES

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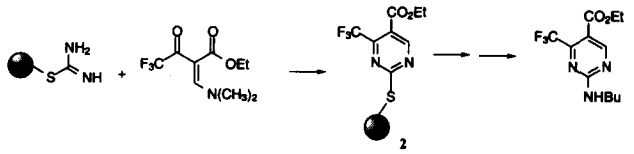
2. Sucholeiki, I. *Tetrahedron Lett.*, **1994**, *35*, 7307 - 7310.
3. Plunkett, M. J.; Ellman, J. A. *J. Org, Chem.* **1995**, *60*, 6006 - 6007, Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999-12000.
4. NovaSyn® TG thiol resin was purchased from Calbiochem-Novabiochem Corp., P.O. Box 12087, La Jolla, CA 92039-2087. Pyrimidine **1** is also commercially available from Ryan Scientific, Inc., P.O. Box 845, Isle of Palms, SC 29451-0845.
5. **General Procedure for the Preparation of Compounds 4**. To the NovaSyn® TG thiol resin (2.0 g, 0.25 mmol/g substitution) in DMF (20 mL) was added pyrimidine **1** (0.52 g, 2.5 mmol) followed by triethylamine (0.35 mL, 2.5 mmol). After shaking for 1 hour, the resin was washed with DMF (3 X 30 mL) and CH_2Cl_2 (3 X 30 mL). To the resin in CH_2Cl_2 (25 mL) was added mCPBA (0.43 g, 2.5 mmol), and the reaction was shaken overnight. The resin was washed with CH_2Cl_2 (3 X 30 mL), DMF (2 X 30 mL) and again with CH_2Cl_2 (3 X 30 mL). After drying **3** under vacuum, the resin was divided into 10 portions (each 0.20 g, 0.05 mmol). To each was added CH_2Cl_2 (1 mL) and amine (0.0475 mmol). The reactions were then shaken 24 h, filtered and concentrated. The overall yields and purities are given in Table 1. **Compound 6**: ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 7.38 (s, 1H), 6.32 (m, 1H), 5.82 (m, 1H), 5.75 (m, 1H), 4.62 (d, 2H), 3.41 (m, 2H), 1.20-1.45 (m, 4H), 0.92 (t, 3H); m.p. 136-137°C; HPLC [isochratic, CH_3CN/H_2O, 65:35 (1% TFA)] 97% purity. **Compound 7**: ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 7.38-7.63 (m, 5H), 5.48 (s, 2H), 4.30 (q, 2H), 1.25-1.60 (m, 4H), 0.98 (t, 3H); HPLC [isochratic, CH_3CN/H_2O, 65:35 (1% TFA)] 94% purity.
6. In preliminary studies, we have synthesized the pyrimidine **2** starting from the activated diketoderivative and resin-bound thiourea.



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