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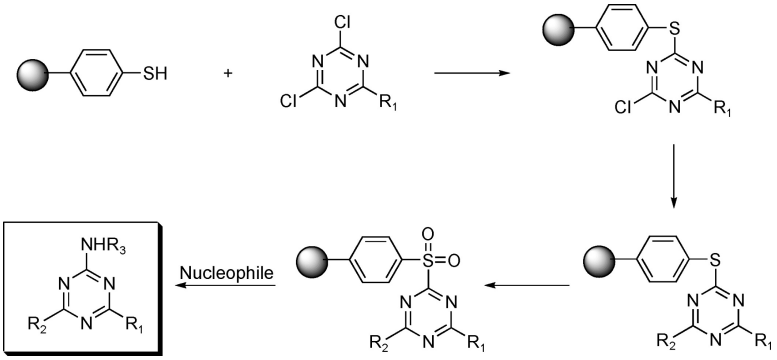

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Safety-Catch Approach to Orthogonal Synthesis of a Triazine Library

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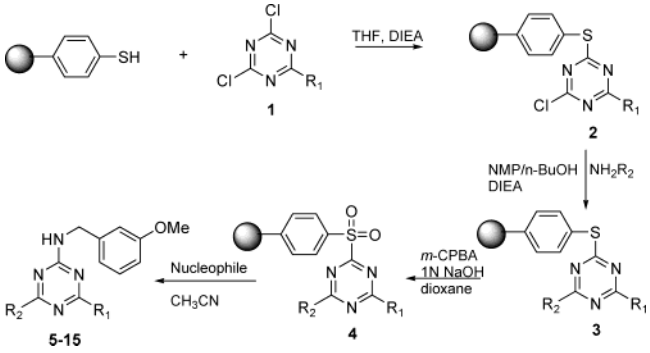
A novel safety-catch method for orthogonal synthesis of highly pure trisubstituted triazines was developed. Since the polymer-support used in this method is not acid-labile, this strategy can be uniquely applied to the synthesis of acid-sensitive triazine library compounds. This method will dramatically increase the diversity of triazine and other related heterocyclic library compounds.

Introduction

Combinatorial chemistry has been a great vehicle for chemists to study cellular functions as well as to search for novel drug candidates. Triazine has elicited considerable interest as a combinatorial library scaffold due to its ease of manipulation and the low price of starting material. Triazine derivatives, the scaffold of which is structurally similar to purine or pyrimidine, have demonstrated a wide range of biological activities.[1] Both the solution and solid-phase syntheses of the triazine libraries have been reported.[2] However, all of the reported syntheses procedures use a stepwise amination approach which results in an accumulation of byproducts yielding impure library compounds at the last stage. Previously, we have developed an orthogonal solid-phase synthetic pathway that yields a highly pure trisubstituted triazine library.[3] Recently, we used this approach to synthesize a tagged triazine library that was used in a forward genetics study to find a novel bioactive compound, encephalazine, and its target proteins.[4] Its derivative, a Boc-containing encephalazine, compound **5**, was found to be even more potent than the mother compound; however, this derivative could not be synthesized directly by our orthogonal solid-phase method, since the Boc group is cleaved during the final acid-catalyzed resin cleavage step. Consequently, we had to resort to solution-phase chemistry for the Boc derivatives.

This drawback in our orthogonal method prompted us to develop an orthogonal safety-catch strategy that allows for solid-phase synthesis of trisubstituted triazines with acid-sensitive moieties (Scheme 1). In our new method, the solid-supported sulfur linker is activated by oxidation to the sulfone, thus allowing for its displacement with an amine nucleophile and releasing the final product from the polymer support.[5] Although similar methods have been previously applied to the purine[6] and pyrimidine[7] scaffolds, this is the first report for orthogonal triazine library synthesis. To demonstrate the robustness of the new method, we have synthesized a set of compounds containing an acid-sensitive Boc or *tert*-butyl ester group with high purity (Table 1). In addition, to assess the scope and limitations of the safety-catch method, we have used a set of amine/aniline/alcohol nucleophiles with various reactivities for the last step product displacement (Table 2). Another drawback in the original orthogonal method is the limited possibility for diversity extension of the linker part of the compound. Once again, the problem lies in the fact that the compounds can only be modified in solution after the solid support cleavage. The new method makes it possible to readily extend the diversity by removing the Boc group and further acylating the compound while still on the solid support (Scheme 2). Thus, to demonstrate the versatility of this method, a set of acylated derivatives was synthesized (Table 3).

Scheme 1. Safety-Catch Method to Synthesize Trisubstituted Triazines



Results and Discussion

PS-Thiophenol resin was used to anchor the monosubstitued triazines, **1**. The second chlorine site was aminated at 120 °C in the presence of *N*,*N*-diisopropylethylamine. It should be noted that during this step, excessive heating or amount of the amine nucleophile will result in the premature displacement of the sulfur solid support. It was found that keeping the reaction temperature at 120 °C and the amount of amine at 7.8 equiv gives the optimal results. We further took advantage of a thioether's property to be oxidized by *m*-CPBA to an activated sulfone, **4**. At this step, care should be taken to keep the reaction pH around 4 by sodium hydroxide addition to protect any acid-labile groups present on the scaffold from being removed. Finally, a nucleophile was used to displace the activated sulfone solid support and release the trisubstituted triazines **5**−**15**. This step was carried out in anhydrous acetonitrile to minimize the amount of the hydrolyzed product, OH-substituted triazine. The purity and

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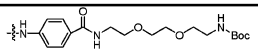
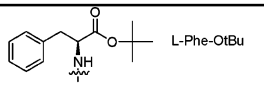
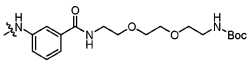
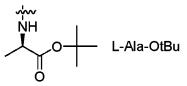
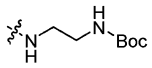
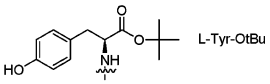
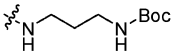
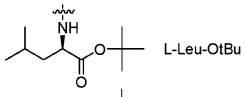
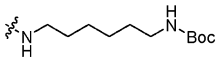
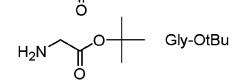
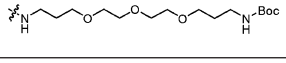
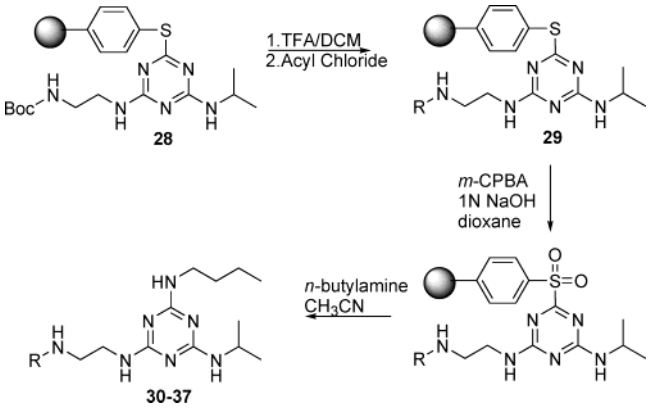
Table 1. Purity of the Final Products

	R_1 =	R_2 =	Purity (%)		R_1 =	R_2 =	Purity (%)
5			95	**11**			97
6			90	**12**			97
7			99	**13**			99
8			>99	**14**			97
9			99	**15**			97
10			99				

Scheme 2. Synthesis of Acylated Derivatives Using Safety-Catch Method



identity of all of the products were monitored by LC/MS and are summarized in Table 1. Small impurities mainly arise from the hydrolysis of the activated sulfone. No Boc or *tert*-butyl removed byproducts were detected.

To evaluate the scope and limitations of the last step, activated sulfone displacement a set of amine, aniline, and alcohol nucleophiles with a broad range of reactivities was used to attack a solid-supported activated form of **16** (Table 2). As expected, amines **17**−**20** resulted in highly pure final products. It was expected that anilines **21**−**23** would not result in a significant amount of product due to their low nuclophilicities. Surprisingly, dimethoxy aniline, **21**, generated moderately pure product, probably due to its electron-donating substituents. Phenol, **24**, was used to determine the reactivity of alcohols toward the activated sulfone; it did not prove to be a suitable nucleophile, with <1% purity of the final product. Both amines **25** and **26** resulted in almost no product. This could be attributed to the tertiary α-carbon rendering these nucleophiles unreactive. Finally, a secondary sterically hindered dibenzylamine, **27**, resulted in only 20% of product.

To extend the diversity of the linker part, compound **28** was subjected to trifluoroacetic acid (TFA)-mediated Boc removal, followed by treatment with a variety of acyl chlorides to result in a compound set, **29** (Scheme 2). Following the general procedure, thioether moiety was further oxidized, and the activated sulfones were displaced by a nucleophile to release acylated derivatives **30**−**37** (Table 3).

In summary, we have developed a safety-catch method for the synthesis of highly pure trisubstituted triazines. Since the polymer-support used in this method is not acid-labile, this strategy can be uniquely applied to the synthesis of acid-sensitive triazine library compounds. Combined with other orthogonal synthesis we have developed,[3,4] this method will dramatically increase the diversity of triazine and other related heterocyclic library compounds.

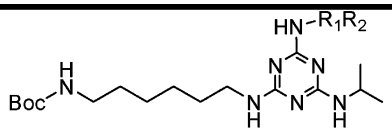
Experimental Section

Coupling of the Thiophenol Resin with a Monosubstituted Triazine. To the suspension of the PS-thiophenol resin (20 mg, 25.6 μmol, purchased from Argonaut Technologies Inc., Lot No. 00729) in tetrahydrofuran (THF) (2 mL) were added a variety of monosubstituted triazines,[4] **1** (20 mg, 96.6 μmol), followed by addition of *N*,*N*-diisopropylethylamine (DIEA) (40 μL, 0.31 mmol). The reaction was placed in a heating block set at 65 °C for 3 h. The solvents and excess reagents were filtered through a PE frit cartridge and washed with DMF, DCM, and MeOH (3 mL × 3), consecutively, ending with a final washing with DCM (3 mL), and dried under nitrogen gas.

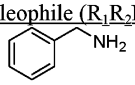
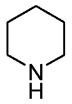
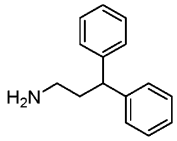
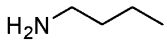
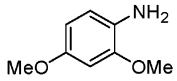
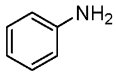
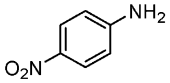
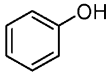
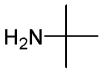
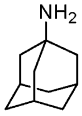
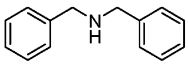
Second Chlorine Substitution. To a suspension of the resin, **2**, in *N*-methyl-2-pyrrolidinone (NMP) (1 mL) and *n*-butanol (1 mL) were added a variety of amines (NH_2R_2) (0.2 mmol), followed by the addition of DIEA (40 μL, 0.31 mmol). The reaction was placed in a heating block set at 120 °C for 3 h. The excess reagents were filtered through a PE frit cartridge and washed with DMF, DCM, and MeOH (1 mL × 3), consecutively, ending with a final washing with DCM (1 mL).

Activation of Final Substitution Site by Oxidation of Thioether to Sulfone. To a solution of *m*-CPBA (balanced with 3-chlorobenzoic acid, 70−75%) (56 mg, 0.23 mmol) in 1,4-dioxane (1.8 mL) was added an aqueous solution of 1 N NaOH (40 μL). This solution was added to the resin, **3**, and gently shaken for 4 h at room temperature. The solution was then filtered out with a PE frit cartridge and washed with 1,4-dioxane (3 mL × 3) and DCM (3 mL × 3),

Table 2. Scope of the Safety-Catch Method



16

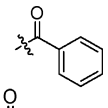
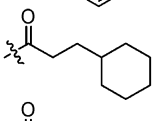
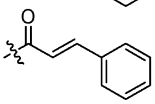
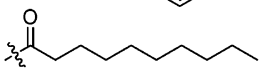
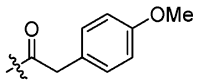
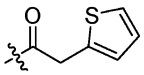
	Nucleophile (R_1R_2NH)	Purity (%)
17		97
18		96
19		90
20		85
21		75
22		20*
23		trace*
24		trace*
25		trace*
26		trace*
27		20*

* The rest is hydrolyzed product and starting material nucleophile.

alternatively, ending with a final washing with DCM (3 mL), and dried under nitrogen gas.

Product Displacement from the Activated Sulfone Support by a Nucleophile. To a suspension of the activated sulfone resin, **4** or **16**, in anhydrous acetonitrile (2 mL) was added PS-DIEA resin (2 mg, purchased from Argonaut Technologies Inc., Lot No. 01688) and a nucleophile (12.8 μmol). The reaction vessel was purged with nitrogen gas and was placed in a heating block set at 90 °C for 8 h. The resin was filtered through a PE frit cartridge and washed with DCM (1 mL × 3). The solvent from the eluent was removed in vacuo, and the products, **5**−**15** and **17**−**27**, were dried under the nitrogen gas.

Table 3. Purity of the Acylated Derivatives

	R	Purity (%)
30		87
31		93
32		93
33		70
34		90
35		90
36		85
37		93

Acyl Derivatives. Compound **28** (40 mg) was dissolved in 2 mL of 10% TFA in DCM and stirred for 3 h at room temperature. The Boc-removed resin was then filtered and washed thoroughly with DMF, MeOH, and DCM and dried under nitrogen gas. Resin (5 mg for each acyl chloride) was suspended in NMP (1 mL) and 5 equiv of pyridine. Acyl chlorides (5 equiv) were then added, and the resin was stirred at room temperature for 3 h. The resulting resins **29** were then filtered and washed thoroughly with DMF, MeOH, and DCM and dried under nitrogen gas. Final acyl derivatives **30**−**37** were obtained after further oxidation and solid-support displacement of the intermediates **29** following the general procedures.

Acknowledgment. We thank the National Institute of Health (CA-96912) for financial support of this work.

Supporting Information Available. Materials used, characterization of representative compounds by ^{1}H NMR, as well as LC/MS traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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