ORGANIC LETTERS

2003
Vol. 5, No. 2
117−120

Novel Orthogonal Strategy toward Solid-Phase Synthesis of 1,3,5-Substituted Triazines

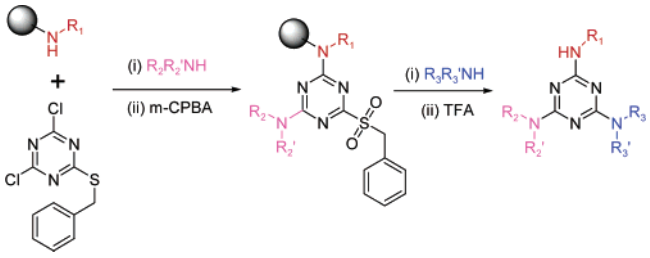
Jacqueline T. Bork, Jae Wook Lee, Sonya M Khersonsky, Ho-Sang Moon, and Young-Tae Chang*

Department of Chemistry, New York University, New York, New York 10003

yt.chang@nyu.edu

Received October 29, 2002

ABSTRACT



To improve upon the previous orthogonal method for synthesis of a triazine library, an alternative strategy has been developed via oxidation-activation of the thioether to the sulfone. Through a comparison between these two methods, the sulfone strategy was demonstrated as an enhanced method in the generation of highly pure triazine library compounds.

Triazine derivatives have demonstrated a broad range of biological activities, including anti-angiogenesis,[1] herbicidal effects,[2] anti-metastatic effects,[3] Erm methyltransferase inhibition,[4]and anti-microbial effects.[5] With the advent of combinatorial chemistry, several triazine libraries have been published in the literature, both in solid[6] and solution[7] phase, taking advantage of its easy manipulation and the low price of starting material. However, all of the reported procedures contain stepwise amination, which is difficult to generalize for nucleophiles with varying reactivities, and thus each reaction step may accumulate byproducts, yielding impure library compounds.[6,7]

We have recently developed a unique orthogonal solid-phase synthetic pathway for a highly pure trisubstituted triazine library, in which certain members of the library exhibited anti-tubulin activity.[8] In this synthetic approach, three types of building blocks were prepared separately and assembled by chemically orthogonal reactions (Figure 1). Although the strategy worked very nicely, giving highly pure triazine library compounds, two problems were encountered.

(1) Ono, M.; Kawahara, N.; Goto, D.; Wakahayashi, Y.; Ushiro, S.; Yoshida, S.; Izumi, H.; Kuwano, M.; Sato, Y. *Cancer Res.* **1996**, *56*, 1512−1516.

(2) Draber, W.; Tietjen, K.; Kluth, J. F.; Trebst, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1621−1633.

(3) Maeda, M.; Iogo, M.; Tsuda, H.; Fujita, H.; Yonemura, Y.; Nakagawa, K.; Endo, Y.; Sasaki, T. *Anti-Cancer Drug Des.* **2000**, *15*, 217−223.

(4) Hajduk, P. J.; Dinges, J.; Schkeryantz, J. M.; Janowick, D.; Kaminski, M.; Tufano, M.; Augeri, D. J.; Petros, A.; Nienaber, V.; Zhong, P.; Hammond, R.; Coen, M.; Beutel, B.; Katz, L.; Fesik, S. W. *J. Med. Chem.* **1999**. *42*, 3852−3859.

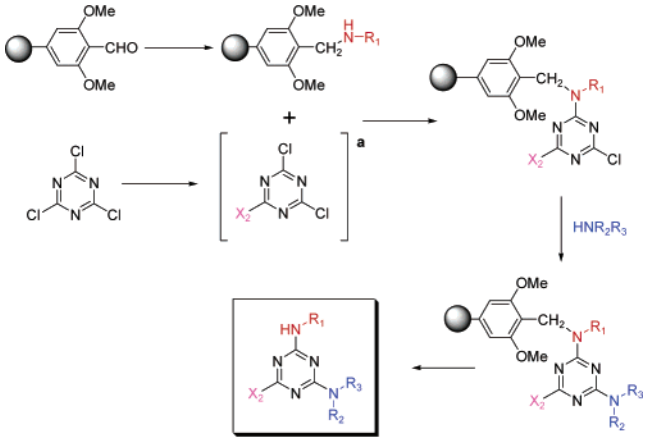
(5) Silen, J. L.; Lu A. T.; Solas, D. W.; Gore, M. A.; MacLean, D.; Shah, N. H.; Coffin, L. M.; Bhinderwala, N. S.; Wang, Y.; Tsutsui, K. T.; Look, G. C.; Campbell, D. A.; Hale, R. L.; Navre, M.; Deluca-Flaherty, C. R. *Antimicrob. Agents Chemother.* **1998**, *42*, 1447−1453.

(6) (a) Stankova, M.; Lebl, M. *Mol. Diversity* **1996**, *2*, 75−80. (b) Scharn, D.; Wenschuh, H.; Reineke, U.; Schneider-Mergener, J.; Germeroth, L. *J. Comb. Chem.* **2000**, *2*, 361−369. (c) Teng, S. F.; Sproule, K.; Hussain, A.; Lowe, C. R. *J. Mol. Recognit.* **1999**, *12*, 67−75. (d) Filippusson, H.; Erlendsson, L. S.; Lowe, C. R. *J. Mol. Recognit.* **2000**, *13*, 370−381.

(7) (a) Gustafson, G. R.; Baldino, C. M.; O'Donnel, M. E.; Sheldon, A.; Tarsa, R. J.; Verni, C. J.; Coffen, D. L. *Tetrahedron* **1998**, *54*, 4051−4065. (b) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097−4106. (c) Falorni, M.; Giacomelli, G.; Mameli, L.; Pordheddu, A. *Tetrahedron Lett.* **1998**, *39*, 7607.

(8) Moon, H.; Jacobson, E.; Khersonsky, S. M.; Luzung, M.; Walsh, D.; Xiong, W.; Lee, J. W.; Parikh, P.; Lam, J. C.; Kang, T. W.; Rosania, G. F.; Schier, A.; Chang, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 11608−11609.

10.1021/ol027195v CCC: $25.00
Published on Web 01/01/2003



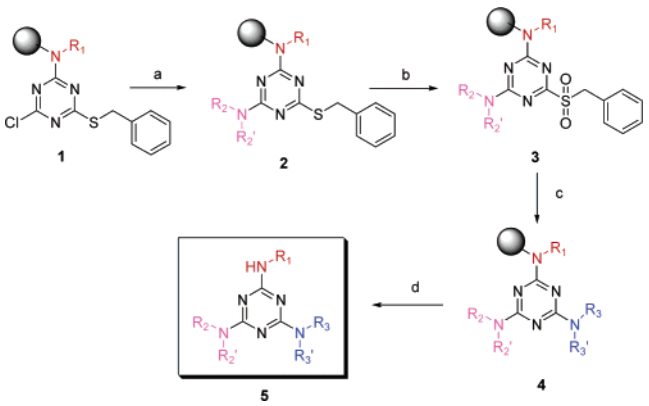
[a] Purification was required via crystallization or column chromatography

Figure 1. Previous orthogonal strategy for 1,3,5-trisubstituted triazines.

First of all, one out of the three building blocks should be prepared by solution-phase chemistry and must be purified either by crystallization or chromatography, which is a cumbersome step for some functionalities. A second problem was found in the extension of the diversity in the last amination step; the low reactivity of the third chloride inhibits the reaction with moderately weak nucleophilic amines. Herein, we report a new orthogonal pathway that can improve the problems of our previous strategy.

To surmount the impediments of the previous orthogonal scheme, we designed a novel orthogonal pathway incorporating an oxidation-activation of a thioether group (Scheme 1). After a primary amine was coupled to 4-formyl-3-dimethoxyphenoxymethyl-functionalized polystyrene resin (PAL) by reductive amination,[9] 2-benzylsulfanyl-4,6-dichloro-[1,3,5]-triazine, synthesized in solution,[10] was loaded on the solid support to give the first building block, **1**. A subsequent amination reaction of **1** with primary or secondary amines introduced a second building block to the chloride position to provide intermediate **2**.

Scheme 1. New Orthogonal Approach toward 1,3,5-Trisubstituted Triazine Library[a]



[a] Reagents and conditions: (a) $NHR_2R'_2$ (20 equiv), DIPEA (20 equiv), BuOH/NMP (1:1), 120 °C, 3 h. (b) *m*-CPBA (10 equiv), 1 N NaOH, 1,4-dioxane, at pH 4, shaken for 8 h. (c) $NHR_3R'_3$ (20.0 equiv), DIPEA (20 equiv), BuOH/NMP (1:1), 120 °C, 3 h. (d) 10% TFA /DCM, shaken for 30 min at room temperature.

The sulfide intermediate allows for the introduction of yet another substituent, by *m*-CPBA oxidation of the thioether linkage,[11] thus, generating another good leaving group, a heterocyclic sulfone. Generally, sulfone is a better leaving group than chloride, a characteristic that will increase the reactivity at that site.[12] It was found to be important to keep the pH of the reaction approximately at 4. Whereas a lower pH induced the cleavage of the PAL linker, a basic condition resulted in hydroxyl replacement of the sulfone group. It is also recommended to make a fresh sulfone intermediate for the next step, as extended time in storage of the reactive intermediate evoked the hydrolysis of the sulfone. A following amination occurred smoothly to incorporate the third building block amines at the new activated position to generate a trisubstituted triazine **4**. Mild acidic cleavage of the resin bound molecule gave the trisubstituted triazine product, **5**. All products were analyzed for purity and identity by LC-MS equipped with a diode array detector.

Benzenemethanethiol was chosen as the most promising reagent, versus 4-methylbenzenethiol or benzenethiol, because of its great stability during the following amination step. For example, when 4-methylbenzenethiol was tested as a candidate, the following amination with piperidine resulted in a 7% impurity consisting of a disubstituted piperidine, suggesting a premature displacement of the thiol compound.

A thorough comparison of reactivity was assessed between the three different amination reactions on the triazine scaffold correlating to the previous and current orthogonal methods: chlorine as a leaving group in reaction **A**, benzyl sulfone as a leaving group in reaction **B**, and chlorine as a leaving group with benzylsulfanyl as an adjacent substituent in reaction **C** (Table 1). The scope of the two orthogonal combinatorial schemes has been validated by testing 30 amines in each of the three pathways. The same conditions in Scheme 1 were applied to each case.

The following amines represented in Table 1 demonstrate the effectiveness of the new sulfone chemistry. 4-Methoxybenzylamine, a strong nucleophile, displayed high purity in all three reactions. Many of the previously observed weaker nucleophiles showed heightened reactivity in reaction **B**. However, those amines that exhibited products with lower purities were generally secondary, sterically hindered amines, such as dibenzylamine and *N*-butylbenzylamine, entries 11 and 12, respectively. Benzyl sulfone is a bulkier leaving group than chlorine, which appears to create a barrier for

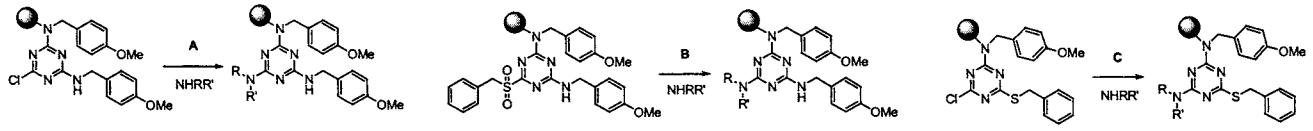
(9) Chang, Y. T.; Gray, N.; Rosania, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T.; Sarohia, R.; Leost, M.; Schultz, P. G. *Chem. Biol.* **1999**, *6*, 361−375.

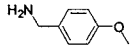
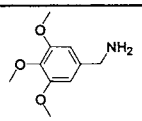
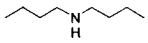
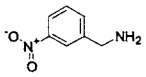
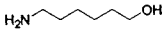
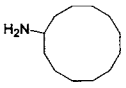
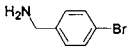
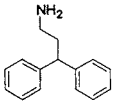
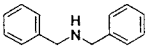
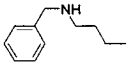
(10) See Supporting Information section for full procedure.

(11) Ding, S.; Gray, G. S.; Ding, Q.; Schultz, P. G. *J. Org. Chem.* **2002**, *66*, 8273−8276.

(12) Guillier, F.; Roussel, P.; Moser, H.; Kane, P.; Bradley, M. *Chem. Eur. J.* **1999**, *5*, 3450−3458.

Table 1. Reactivity Comparison between Three Substitution Reactions



entry	amine	purity (%) A	B	C	entry	amine	purity (%) A	B	C
1		96	99	99	7		81	99	78
2		92	90	99	8		75	95	98
3		95	99	95	9		58	90	96
4		89	93	99	10		81	98	95
5		83	99	92	11		81	38	94
6		89	99	93	12		91	75	99

more sterically hindered nucleophiles. The purities of the benzylsulfanyl triazines from reaction **C** were generally higher than those of the 4-methoxybenzylamine triazines from reaction **A**, suggesting an increased reactivity at the chloro position of the benzylsulfanyl triazine.[13] For those compounds containing hydroxyl groups (i.e., entry 3), a TFA ester formed, which was hydrolyzed by 10% dimethylethylamine in MeOH. The impurities resulting in the reaction are mainly unreacted starting material.

The reactivity data, of which some are shown in Table 1, will be a useful guideline for the selection of the library building blocks for a highly pure triazine library. To demonstrate the practical usefulness of the results and the flexibility of the new orthogonal chemistry, a small library of 96 compounds was constructed and analyzed. Amines were chosen for the second and third aminations, $NHR_2R'_2$ and $NHR_3R'_3$, respectively, on the basis of their compared purities, as illustrated in Table 1. The reaction followed the conditions in Scheme 1, which involved (1) a replacement of chlorine, followed by (2) oxidation and a replacement of sulfone (Figure 2). The average purity of the 96 products was 94%. This result clearly demonstrates the robustness of this new strategy.

In summary, we report a new synthetic strategy toward making 1,3,5-trisubstituted combinatorial triazine libraries.

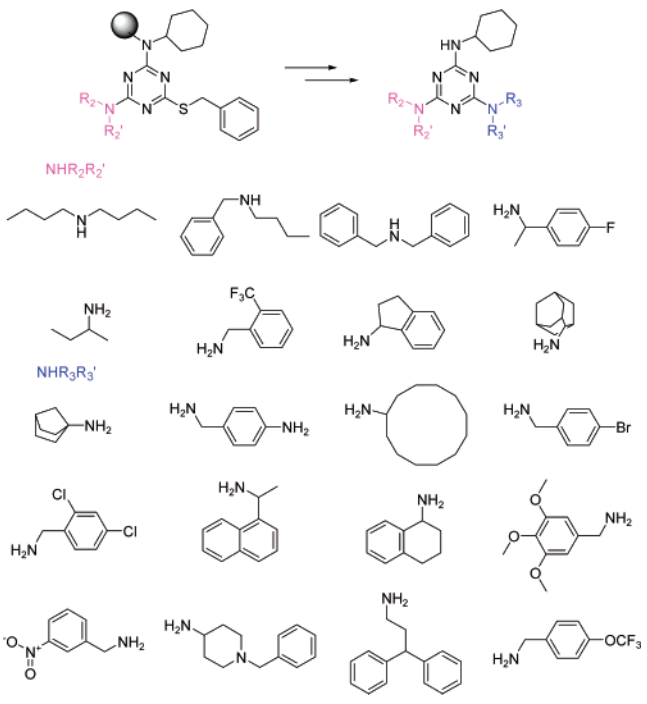


Figure 2. Test synthesis of a small library using new orthogonal chemistry.

(13) Barillari, C.; Barlocco, D.; Raveglia, L. F. *Eur. J. Org. Chem.* **2001**, 4737−4341.

The sulfone chemistry in the combinatorial triazine scheme has the following merits: (1) the difficulty of substituting more unreactive amines at the final step has been improved by using benzylsulfanyl triazine as an intermediate and benzyl sulfone as a leaving group; (2) the overall sulfone scheme provides a more convergent strategy, as the dependence of scaffold diversity on multiple resin-bound amines and variability in solution chemistry has been eliminated; and (3) the flexibility at each amination site gives rise to a greater diversification, broadening the scope of different combinations. The construction of large numbers of library members and their biological screening are in progress.

Acknowledgment. Funding supports from Luminogene (www.luminogene.com) is acknowledged.

Supporting Information Available: Experimental details for the syntheses of the library compounds and representative LC-MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027195V