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Solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxide library

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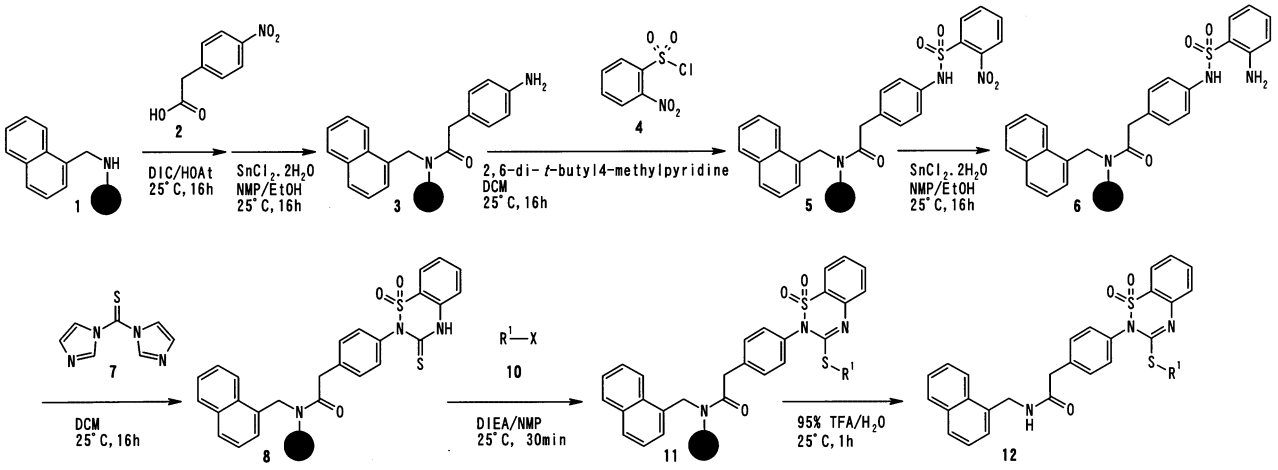
Abstract—The first solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides has been developed. Synthesis of the title compounds was achieved as follows: (1) sulfonylation of solid-supported primary amines with 2-nitrobenzenesulfonylchlorides, (2) reduction of the nitro group, (3) cyclization with thiocarbonyldiimidazole (formation of thiourea), (4) *S*-alkylation or *S*-arylation of the thiourea. In addition to the excellent purity of the product, a large-size library can be synthesized with the method as this synthesis includes three diversity points. © 2002 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry for the synthesis of non-peptide organic compounds has emerged as an important tool for drug discovery.[1] Solid-phase synthesis of substituted heterocyclic compounds, in particular, has been a focus of recent investigations with application toward a variety of drug targets.[2] As part of our project to develop efficient synthetic methods for heterocyclic compounds,[3] the solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides was investigated. Although the structural similarity of 3-(sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxide to other important pharmacophores such as quinazoline-2,4-diones,[3d,4] 4-quinazolinones,[3b,5] 1,2,4-benzothiadiazin-3-one 1,1-dioxides,[6] and 2-thioxoquinazolin-4-ones[3a,c] is fascinating from the viewpoint of new drug discovery, there has been only one report of the synthesis of 3-(sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides in a solution-phase.[7] Therefore, we undertook development of a solid-phase synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides as follows.

First, **1** was prepared by reductive amination of 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin[8] with 1-aminomethylnaphthalene. Although the derivatized



Scheme 1.

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resin **1** was used for all the compounds in this report, various amines can be used for this reductive amination to offer the first diversity point.[9] The solid-supported arylamine **3** was obtained by acylation of **1** with 4-nitrophenylacetic acid **2** and subsequent reduction of the nitro group (Scheme 1). Various solid-supported amines can be prepared using other building blocks instead of **2** as the second diversity point as described later. Next, sulfonylation of **3** using 2-nitrobenzenesulfonyl chloride **4** was examined. Although there have been numerous reports of the preparation of 2-nitrobenzenesulfonamide for the solid-phase Fukuyama–Mitsunobu alkylations,[10] the reaction of **3** with **4** did not give **5** with high purity due to insufficient sulfonylation at 4°C, or disulfonylation (formation of sulfonimides) and other unknown byproduct formations at 25°C. After testing various bases (diisopropylethylamine {DIEA}, pyridine, 2,6-lutidine, 2,4,6-collidine, 2,6-*t*-butylpyridine, 2,6-di-*t*-butyl-4-methylpyridine), solvents (*N*-methylpyrrolid-2-one {NMP}, dichloromethane {DCM}) and reaction temperatures (4-25°C), the sulfonylation with 2,6-di-*t*-butyl-4-methylpyridine/DCM at 25°C was found to give **5** with excellent purity. The bulky 2,6-*t*-butyl group successfully suppressed the sulfonimidation. Then, **5** was treated with $SnCl_2{\cdot}2H_2O$/EtOH/NMP[11] at 70°C to give **6** with high purity. The reduction of the nitro group was not sufficient at 25°C to give a mixture of the nitroso intermediate and **6**. The cyclization of **6** proceeded smoothly with thiocarbonyldiimidazole **7** at 25°C to give **8**. Then, *S*-alkylation of **8** was performed with alkyl halide **10**/DIEA/NMP at 25°C for 30 min to offer the third diversity point. As shown in Table 1, **12** was obtained with high purities and yields using the following alkyl halides:[12] iodomethane (entry a), alkyl bromides with an electron-withdrawing group at the α position (entries b–d), benzyl type bromide (entries e and f), allyl bromide (g), and simple alkyl halide (entries h and i). An S_NAr reaction for arylation also proceeded smoothly using the Sanger reagent (entry j). As the second diversity point, various solid-supported amines **13** were prepared by reaction of **1** with nitrobenzene derivatives followed by treatment with $SnCl_2{\cdot}2H_2O$/EtOH/NMP (Table 2, entries k and l), or with Fmoc-amino acids followed by treatment with 20% piperidine/NMP (entry p) as shown in Scheme 2. 2-Substituted-3-(methylsulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides **15** were obtained with excellent purity using the solid-supported arylamines (entries k–o);

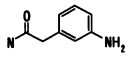
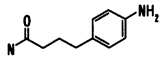
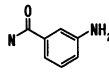
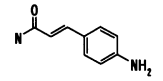
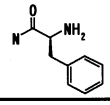
Table 1. Synthesis of 2-[phenyl-*N*-(1-naphthylmethyl)-acetamide]-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides

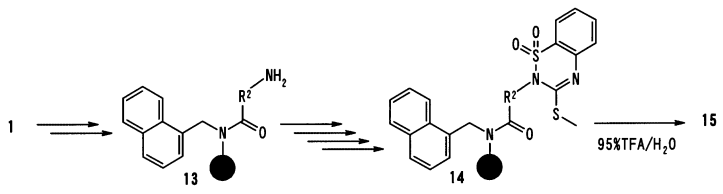
Entry	**10**	**12**	
		Purity (%)[a]	Yield (%)[b]
a	Iodomethane	>95	75
b	Methyl bromoacetate	>95	90
c	2-Bromoacetylnaphthalene	>95	65
d	Propagyl bromide	89	71
e	Benzyl bromide	>95	72
f	2-Bromomethylnaphthalene	>95	67
g	Allyl bromide	93	80
h	Ethyl iodide	93	71
i	Phenoxypropyl bromide	87	65
j	2,4-Dinitrofluorobenzene	>95	63

[a] Reverse-phase HPLC was carried out using water/acetonitrile (0.04% TFA) linear gradients from 5% to 98% organic component over 5 min. Flow rate: 2 mL/min. Column: Waters Symmetry C_{18} (3.5 μm) 4.6×50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210+2*N*) nm, $N=0$–45.

[b] Crude yields based on the theoretical loading weight of target molecules.

Table 2. Synthesis of 2-substituted-3-(methylsulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides from various solid-supported amines

Entry	**13**	**15**	
		purity (%)	yield (%)
k		> 95	75
l		83	75
m		> 95	61
n		93	67
o		> 95	72
p		64	74



Scheme 2.

however, lower purity resulted using the solid-supported phenylalanine (entry p). All the product structures in this manuscript were confirmed by ^{1}H NMR and LC–MS (ESI mass spectrometer).

The solid-phase chemistry for the synthesis of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides was achieved for the first time with excellent purities. Although the variety of sulfonyl chlorides is limited (the third diversity point), a number of reagents are commercially available for amines (the first diversity point), nitrobenzene derivatives with carboxylic acids (the second diversity point), and alkyl halides (the fourth diversity point). Therefore, a large number of 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides can be synthesized using this solid-phase synthesis.

References

1. For reviews, see: (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev*. **1996**, *96*, 555; (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385.
2. (a) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett*. **1996**, *37*, 937; (b) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett*. **1996**, *37*, 5835; (c) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc*. **1992**, *114*, 10997; (d) Buckman, B. O.; Mohan, R. *Tetrahedron Lett*. **1996**, *37*, 4439; (e) Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett*. **1996**, *37*, 7031; (f) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett*. **1998**, *39*, 7235.
3. (a) Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T. *Tetrahderon Lett*. **2000**, *41*, 8333; (b) Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T. *Synlett* **2000**, 1670; (c) Makino, S.; Nakanishi, E.; Tsuji, T. *Tetrahderon Lett*. **2001**, *42*, 1749; (d) Makino, S.; Suzuki, N.; Nakanishi, E.; Tsuji, T. *Synlett* **2001**, 333.
4. (a) Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron Lett*. **1997**, *38*, 1729; (b) Gordeev, M. F.; Luehr, G. W.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron* **1998**, *54*, 15879.
5. Mayer, J. P.; Lewis, G. S.; Curtis, M. J.; Zhang, J. W. *Tetrahedron Lett*. **1997**, *38*, 8445.
6. (a) Patent: EP268990, 1988; (b) Patent: WO9707116, 1997.
7. Chern, J.-W.; Wu, Y.-H.; Liu, K.-C. *J. Heterocyclic Chem*. **1990**, *27*, 1485.
8. 4-(4-Formyl-3-methoxyphenoxy)butyryl AM resin (100–200 mesh, loading 0.53 mmol/g) was purchased from Novabiochem (http://www.nova.ch).
9. The following amines were used for this reductive amination and subsequently acylated with **2** to give the corresponding 2-substituted-3-(substituted sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxides: isopropylamine, allylamine, cyclobutylamine, furfurylamine, piperonylamine, phenethylamine, 2,2-diphenylethylamine.
10. (a) Yang, L.; Chiu, K. *Tetrahedron Lett*. **1997**, *38*, 7307; (b) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett*. **1998**, *39*, 1243; (c) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc*. **1998**, *120*, 2690.
11. (a) Kiselyov, A. S.; Armstrong, R. W. *Tetrahedron Lett*. **1997**, *35*, 6163; (b) Zaragoza, F.; Stephensen, H. *J. Org. Chem*. **1999**, *64*, 2555.
12. *General procedure for the preparation of* ***12a***: 4-(4-Formyl-3-methoxyphenoxy)butyryl AM resin (NOVAbiochem, 100–200 mesh, loading 0.53 mmol/g, 60 mg) was put into a 2.5 mL syringe fitted with a polyethylene filter. 1-Aminomethylnaphthalene/$NaCNBH_3$/NMP/AcOH (150 μL/32 mg/1.0 mL/10 μL) was added to the syringe, and the syringe was shaken for 16 h at 25°C, then for 6 h at 50°C.[13] The resin was washed with MeOH (2 mL×3), DMF (2 mL×3) and DCM (2 mL×3), and dried under vacuum for 3 h. After 4-nitrophenylacetic acid (73 mg) was pre-activated with *N*,*N*′-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt)/NMP (29 μL/55 mg/1.2 mL) at 25°C for 1 h, this solution was added to the syringe and the syringe was shaken at 25°C for 16 h. The resin was washed with DMF (2 mL×3) and DCM (2 mL×3), and dried under vacuum for 3 h. The resin was treated with $SnCl_2{\cdot}2H_2O$/NMP/EtOH (1.0 g/2.0 mL/0.1 mL) at 25°C for 16 h, and washed with DMF (2 mL×3), DCM (2 mL×3), and dried under vacuum for 3 h. 2 - Nitrophenylsulfonylchloride/2,6 - *t* - butyl - 4 - methylpyridine/DCM (100 mg/300 μL/1 mL) was added to the syringe, and the syringe was shaken for 16 h at 25°C. The resin was washed with DMF (2 mL×3) and DCM (2 mL×3), and dried under vacuum for 3 h. Then, $SnCl_2{\cdot}2H_2O$/NMP/EtOH (1.0 g/2.0 mL/0.1 mL) was added to the syringe and it was shaken at 70°C for 16 h. After the resin was washed with DMF (2 mL×3) and DCM (2 mL×3), thiocarbonyldiimidazole/DCM (100 mg/1 mL) was added to the syringe, and the syringe was shaken at 25°C for 16 h. After being dried under vacuum for 3 h, the resin was treated with iodomethane/DIEA/NMP (140 μL/344 μL/2 mL) at 25°C for 30 min, then washed with DMF (2 mL×3) and DCM (2 mL×3) and dried under vacuum for 3 h. Finally, the resin was treated with 95% trifluoroacetic acid (TFA)/H_2O for 1 h and the solution was concentrated.[14] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the crude product **12a** (14.3 mg, yield 84% based on the theoretical loading weight of **12a**). ^{1}H NMR (Varian VXR-300S, 300 MHz, DMSO-d_6): δ 8.71 (t, J=5.4 Hz, 1H), 8.01–8.04 (m, 1H), 7.92–7.97 (m, 2H), 7.81–7.88 (m, 2H), 7.41–7.61 (m, 9H), 4.76 (d, J=5.4 Hz, 2H), 3.61 (s, 2H), 2.49 (s, 3H). ESIMS m/z 502 $[MH]^+$.
13. FlexChem rotating oven, Model 404 (http://www.robsci.com).
14. Genevac HT-8 available from Genevac Limited (Farthing Road, Ipswich, IP1 5AP, UK).