Notes

Efficient Solid-phase Synthesis of 2,1,3-Benzothiadiazin-4-one 2-Oxides with SynPhase™ Lanterns

Shingo Makino,* Eiji Nakanishi, and Takashi Tsuji

Pharmaceutical Research Laboratories, Ajinomoto Co., Inc. 1-1, Suzuki-cho, Kawasaki-ku, Kawasaki-shi 210-8681, Japan
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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 a part of our project to develop efficient synthetic methods for heterocycles,[3] we have investigated the solid-phase synthesis of 2,1,3-benzothiadiazin-4-one 2-oxides as they are similar to other important heterocycles such as quinazoline-2,4-diones,[3d,4] 2-thioxoquinazolin-4-ones,[3a,3e] 4-quinazolinones,[3b,5] 1,2,4-benzothiadiazine 1,1-dioxide,[3e] 1,2,4-benzothiadiazin-3-one 1,1-dioxide,[3f] benzimidazole,[6] hydantoin,[7] 2-piperazinone[8] Since these heterocycles have been prepared from solid-supported primary amines including nitrogen atoms as parts of the heterocycles, they can easily be compared to bioactivities of 2,1,3-benzothiadiazin-4-one 2-oxides by developing the appropriate solid-phase chemistry (Figure 1). Nevertheless, to the best of our knowledge, there has been only one report of the synthesis of 2,1,3-benzothiadiazin-4-one 2-oxides in solution-phase.[9] 2,1,3-Benzothiadiazin-4-one 2-oxides were synthesized by reacting 2-(alkylamino)benzamides with conc. thionylchloride under reflux in the previous report; however, this reaction is not suitable for our solid-phase synthesis as the compounds on solid-support would be cleaved under such acidic condition. Thus, investigation was required for thionylation on solid-support. In addition, preparation of diverse 2-(alkylamino)benzamide was difficult with the reported method; therefore, we decided to prepare 2-(alkylamino)-benzamides from 2-fluoro-5-nitrobenzamides through S_NAr reaction. The key building block, 2-fluoro-5-nitrobenzoic acid, was successfully applied to the solid-phase synthesis of various heterocycles, such as benzimidazoles,[10] benzopiperazinones,[11] macrocycles,[12] 1,4-benzothiazepin-5-ones,[13] quinazoline-2,4-diones,[3d] 2-thioxoquinazolin-4-ones.[3e] Here, we report the solid-phase synthesis of 2,1,3-benzothiadiazin-4-one 2-oxides.

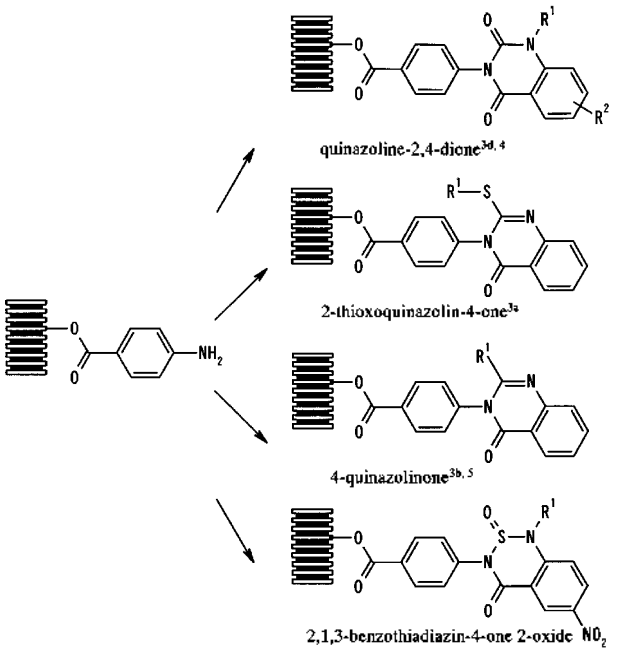
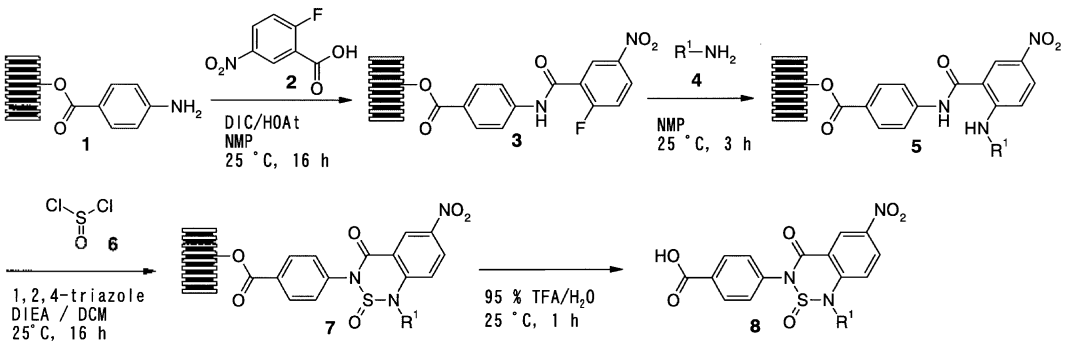


Figure 1. Examples of heterocycles that have been synthesized on SynPhase™ Lantern.

SynPhase™ Lantern[14] bearing 4-aminobenzoic acid ester **1** was prepared as previously described.[3a] Then, **1** was reacted with 2-fluoro-5-nitrobenzoic acid **2** activated with N,N'-diisopropylcarbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt). Preactivation of **2** is important to prevent solid-supported amine **1** from reacting with **2** or DIC. S_NAr type reaction was performed by treating **3** with various primary amines **4** to give **5** with high purity. Next, cyclization of **5** was attempted using thionylchloride **6**. Although various reaction conditions such as the base (diisopropylethylamine {DIEA}, pyridine, 2,6-lutidine, 2,4,6-collidine), solvents (dichloromethane {DCM}, THF, 1,4-dioxane) and reaction temperature (0-25 °C) were examined, **7** was obtained together with unknown byproducts. Therefore, thionylchloride was converted into more stable reagents with several additives (tetrazole, 1,2,4-triazole, imidazole) prior to the addition to the Lantern, and the treatment of **5** with thionylchloride/1,2,4-triazole/DIEA/DCM was found to give 2,1,3-benzo-

*Corresponding author. Phone: +81-44-210-5826; Fax: +81-44-210-5876; E-mail: shingo_makino@ajinomoto.com



Scheme 1. Synthetic scheme for 2,1,3-Benzothiadiazin-4-one 2-oxides.

thiadiazin-4-one 2-oxides **8** in high purity. (Table 1, Entry a-h). In addition, various solid-supported arylamines prepared from the corresponding nitrobenzenes were derivatized by the same procedure to give 2,1,3-benzothiadiazin-4-one 2-oxides in high purity (Entry i-l), showing the procedure is suitable for an array of compounds. Furthermore, the nitro group at the 6-position of 2,1,3-benzothiadiazin-4-one 2-oxides was successfully reduced with $SnCl_2{\cdot}2H_2O$/EtOH/NMP to offer the additional diversity point.[16]

In conclusion, the solid-phase synthesis of 2,1,3-benzothiadiazin-4-one 2-oxides has been successfully achieved for the first time. Various 2,1,3-benzothiadiazin-4-one 2-oxides can be synthesized with high purity. In addition, bioactivities of 2,1,3-benzothiadiazin-4-one 2-oxides can be efficiently compared with those of other important pharmacophores as described above.

General procedure for preparation of 4-(2-oxido-4-oxo-1-propyl-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)benzoic acid (8a). SynPhase™ lantern (SP-PS-D-HMP, loading 35 μmol/lantern) bearing the 4-aminobenzoic acid ester was put into 2.5-mL syringe. After 2-fluoro-5-nitrobenzoic acid (1.0 mmol) was activated with DIC/HOAt / NMP (0.5 mmol/1.0 mmol/2 mL) at 25 °C for 1 h, this solution was added to the syringe. After shaking the syringe for 16 h, the resin was washed with dry DMF (2 mL × 3) and dry DCM (2 mL × 3), and dried under a vacuum for 1 h. After isopropylamine/NMP (200 mL/1.0 mL) was added, the syringe was shaken for 3 h and the resin was washed with DMF (2 mL × 3) and DCM (2 mL × 3). Then, the mixture of thionyl chloride/triazole/DIEA/DCM (80 uL/250 mg/400 uL/1 mL) was added to the syringe, and the syringe was shaken for 16 h. After washing the resin with DCM (2 mL × 2), DMF (2 mL × 3) and DCM (2 mL × 3), the resin was dried under a vacuum for 3 h. The resin was treated with 95% TFA/H_2O for 1 h and the filtrate was concentrated with Genevac evaporator. The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the crude product.

(11.7 mg, yield 86%) ^{1}H NMR (Varian VXR-300S, 300 MHz, DMSO-d_6) δ 8.85 (d, J = 2.7 Hz, 1H), 8.57 (dd, J = 9.2, 2.7 Hz, 1H), 8.13 (dt, J = 8.7, 2.1 Hz, 2H), 7.72 (d, J = 9.2 Hz, 1H), 7.60 (dt, J = 8.7, 2.1 Hz, 2H), 4.28 (dt, J = 14.7, 6.3 Hz, 1H), 4.0 (dt, J = 14.7, 7.7 Hz, 1H), 1.80-1.71 (m, 2H), 0.95(t, J = 7.3 Hz, 3H). ESIMS *m/z* 390 $[M+H]^+$.

4-(1-Allyl-2-oxido-4-oxo-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)benzoic acid (8b). Prepared as described above, using allylamine. (11.1 mg, yield 82%) ^{1}H NMR (DMSO-d_6) δ 8.45 (d, J = 3.0 Hz, 1H), 8.59 (dd, J = 3.0, 9.0 Hz, 1H), 8.15 (dt, J = 8.7 Hz, 2.1, 2H), 7.63 (dt, J = 8.7, 2.1 Hz, 2H), 7.59 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 6.6 Hz, 1H), 6.09-5.98 (m, 1H), 5.44 (dd, J = 16.2, 2.8 Hz, 1H), 5.35 (dd, J = 11.7, 2.8 Hz, 1H), 4.94-4.76 (m, 2H). ESIMS *m/z* 388 $[M+H]^-$.

4-(1-Isobutyl-2-oxido-4-oxo-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)benzoic acid (8c). Prepared as described above, using isobutylamine. (10.3 mg, yield 73%) ^{1}H NMR (DMSO-d_6) δ 8.86 (d, J = 2.7 Hz, 1H), 8.56 (dd, J = 9.3, 2.7 Hz, 1H), 8.14 (dt, J = 8.7, 2.1 Hz, 2H), 7.77 (d, J = 9.6 Hz, 1H), 7.58 (dt, J = 8.7, 2.1 Hz, 2H), 4.29 (dd, J = 14.9, 5.0 Hz, 1H), 3.75 (dd, J = 14.9, 9.6 Hz, 1H), 2.18-1.94 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H). ESIMS *m/z* 404 $[M+H]^-$.

4-(1-Cyclopropyl-2-oxido-4-oxo-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)benzoic acid (8d). Prepared as described above, using cyclopropylamine. (12.6 mg, yield 93%) ^{1}H

Table 1. Synthesis of 2,1,3-Benzothiadiazin-4-one 2-oxides using various amines **4** and several derivatized Lanterns

Entry	Solid-supported amine **1**	amine **4**	**8** purity[a] (%)	**8** yield[b] (%)
a	4-aminobenzoic acid	*n*-propylamine	>95	86
b	4-aminobenzoic acid	allylamine	>95	82
c	4-aminobenzoic acid	isobutylamine	>95	73
d	4-aminobenzoic acid	cyclopropylamine	>95	93
e	4-aminobenzoic acid	cyclobutylamine	>95	96
f	4-aminobenzoic acid	cyclohexanemethylamine	>95	87
g	4-aminobenzoic acid	4-phenylbutylamine	>95	91
h	4-aminobenzoic acid	piperonylamine	>95	72
i	3-aminobenzoic acid	*n*-propylamine	>95	79
j	2-aminocinnamic acid	*n*-propylamine	>95	87
k	3-aminocinnamic acid	*n*-propylamine	91	99
l	4-aminocinnamic acid	*n*-propylamine	83	97

[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 mm) 4.6 × 50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210–350) nm. [b]Crude yields based on the theoretical loading weight of target molecules.

NMR (DMSO-d_6) δ 8.82 (d, J = 3.0 Hz, 1H), 8.66 (dd, J = 9.0, 3.0 Hz, 1H), 8.12 (dt, J = 8.7, 2.1 Hz, 2H), 7.91 (d, J = 9.0 Hz, 1H), 7.63 (dt, J = 8.7, 2.1 Hz, 2H), 3.29-3.21 (m, 1H), 1.34-1.20 (m, 3H), 0.86-0.79 (m, 1H). ESIMS m/z 388 $[MH]^+$.

4-(1-Cyclobutyl-2-oxido-4-oxo-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)benzoic acid (8e). Prepared as described above, using cyclobutylamine. (13.5 mg, yield 96%) ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 2.9 Hz, 1H), 8.56 (dd, J = 9.3, 2.9 Hz, 1H), 8.13 (dt, J = 8.7, 2.1 Hz, 2H), 7.64 (dt, J = 8.7, 2.1 Hz, 2H), 7.55 (d, J = 9.3 Hz, 1H), 4.66 (tt, J = 8.0 Hz, 1H), 2.61-2.19 (m, 4H), 1.95-1.86 (m, 2H). ESIMS m/z 402 $[MH]^+$.

4-[1-(Cyclohexylmethyl)-2-oxido-4-oxo-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl]benzoic acid (8f). Prepared as described above, using cyclohexanemethylamine. (13.5 mg, yield 87%) ^{1}H NMR (DMSO-d_6) δ 8.85 (d, J = 2.7 Hz, 1H), 8.57 (dd, J = 9.2, 2.7 Hz, 1H), 8.14 (dt, J = 8.6, 2.1 Hz, 2H), 7.76 (d, J = 9.2 Hz, 1H), 7.57 (dt, J = 8.6, 2.1 Hz, 2H), 4.27 (dd, J = 15.1, 4.5 Hz, 1H), 3.82 (dd, J = 15.1, 9.1 Hz, 1H), 1.84-1.58 (m, 6H), 1.28-0.94 (m, 5H). ESIMS m/z 444 $[MH]^+$.

4-[2-Oxido-4-oxo-1-(4-phenylbutyl)-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl]benzoic acid (8g). Prepared as described above, using 4-phenylbutylamine. (15.3 mg, yield 91%) ^{1}H NMR (DMSO-d_6) δ 8.84 (d, J = 3.0 Hz, 1H), 8.56 (dd, J = 9.1, 2.5 Hz, 1H), 8.11 (dt, J = 6.9, 2.0 Hz, 2H), 7.69 (d, J = 9.6 Hz,1H), 7.62 (dt, J = 8.7, 2.0 Hz, 1H), 7.54 (dt, J = 8.7, 2.0 Hz, 2H), 7.23 (d, J = 6.9 Hz, 2H), 7.17-7.13 (m, 2H), 4.37-4.27 (m, 2H), 4.15-4.05 (m, 1H), 2.65-2.58 (m, 2H), 1.79-1.59 (m, 4H). ESIMS m/z 480 $[MH]^+$.

4-[1-(1,3-Benzodioxol-5-ylmethyl)-2-oxido-4-oxo-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl]benzoic acid (8h). Prepared as described above, using piperonylamine. (12.1 mg, yield 72%) ^{1}H NMR (DMSO-d_6) δ 8.83 (d, J = 2.8 Hz, 1H), 8.53 (dd, J = 9.1, 2.8 Hz, 1H), 8.14 (dt, J = 8.4, 2.2 Hz, 2H), 7.66-7.56 (m, 3H), 7.04 (d, J = 1.5 Hz, 1H), 6.98-6.90 (m, 2H), 6.56 (dt, J = 9.0, 2.2 Hz, 1H), 6.01 (dd, J = 0.9, 3.3 Hz, 2H), 5.32 (s, 2H). ESIMS m/z 482 $[MH]^+$.

3-(2-Oxido-4-oxo-1-propyl-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)benzoic acid (8i). Prepared as described above, using 3-aminobenzoic acid. (10.8 mg, yield 79%) ^{1}H NMR (DMSO-d_6) δ 8.85 (d, J = 3.0 Hz, 1H), 8.57 (dd, J = 9.3, 2.7 Hz, 1H), 8.12-8.08 (m, 1H), 7.98-7.96 (m, 1H), 7.74-7.70 (m, 3H), 4.27 (dt, J = 14.7, 7.5 Hz, 1H), 4.01 (dt, J = 14.7, 7.5 Hz, 1H), 1.83-1.72 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H). ESIMS m/z 390 $[MH]^+$.

(2E)-3-[2-(2-Oxido-4-oxo-1-propyl-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)phenyl]-2-propenoic acid (8j). Prepared as described above, using 2-aminocinnamic acid. (14.1 mg, yield 97%) ^{1}H NMR (DMSO-d_6) δ 8.85 (d, J = 3.0 Hz, 1H), 8.57 (dd, J = 9.3, 2.7 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.80 (s, 1H), 7.73-7.61 (m, 3H), 7.49 (dd, J = 7.5, 0.9 Hz, 1H), 6.63 (d, J = 16.2 Hz, 1H), 4.26 (dt, J = 15.0, 7.3 Hz, 1H), 4.00 (dt, J = 15.0, 7.3 Hz, 1H), 1.84-1.72 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H). ESIMS m/z 416 $[MH]^+$.

(2E)-3-[3-(2-Oxido-4-oxo-1-propyl-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)phenyl]-2-propenoic acid (8k). Prepared as described above, using 3-aminocinnamic acid. (14.4 mg, yield 99%) ^{1}H NMR (DMSO-d_6) δ 8.83 (dd, J = 8.2, 2.9 Hz, 1H), 8.59 (dd, J = 9.0, 2.9 Hz, 1H), 8.07 (dd, J = 9.0, 2.7 Hz, 1H), 7.76 (dd, J = 9.0, 4.6 Hz, 1H), 7.69-7.61 (m, 2H), 7.54-7.43 (m, 2H), 6.63 (d, J = 15.9 Hz, 1H), 4.27 (dt, J = 14.7, 6.0 Hz, 1H), 3.98 (dt, J = 14.7, 7.5 Hz, 1H), 1.82-1.71 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ESIMS m/z 416 $[MH]^+$.

(2E)-3-[4-(2-Oxido-4-oxo-1-propyl-1,4-dihydro-3H-2,1,3-benzothiadiazin-3-yl)phenyl]-2-propenoic acid (8l). Prepared as described above, using 4-aminocinnamic acid. (12.6 mg, yield 97%) ^{1}H NMR (DMSO-d_6) δ 8.85 (d, J = 3.0 Hz, 1H), 8.57 (dd, J = 9.3, 2.7 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 15.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 15.9 Hz, 1H), 4.27 (dt, J = 14.9, 6.3 Hz, 1H), 4.00 (dt, J = 14.9, 7.5 Hz, 1H), 1.80-1.71 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ESIMS m/z 416 $[MH]^+$.

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14. SynPhase™ Lanterns are available from Mimotopes (Clayton, Victoria, Australia). The type of Lantern used in this communi-

cation was SP-PS-D-HMP (long-chain hydroxymethyl phenoxy linker), loading 35 mmol/Lantern.

15. Representative Procedure for **8a**. The 4-aminobenzoic acid ester bearing SynPhase™ Lantern (SP-PS-D-HMP, loading 35 μmol/Lantern)[14] was placed into a 2.5-mL syringe without a filter. After 2-fluoro-5-nitrobenzoic acid (1.0 mmol) was activated with DIC/HOAt/NMP (0.5 mmol/1.0 mmol/2 mL) at 25 °C for 1 h, the Lantern was treated with this solution for 16 h. The Lantern was washed with dry DMF (2 mL × 3) and dry DCM (2 mL × 3), and dried under a vacuum for 1h. After n-propylamine/NMP (200 uL/1.0 mL) was added to the Lantern, the Lantern was shaken for 3 h and washed with DMF (2 mL × 3) and DCM (2 mL × 3). Then, to the syringe was added the mixture of thionyl chloride/1,2,4-triazole/DIEA/DCM (80 uL/250 mg/400 uL/1 mL), and it was shaken for 16 h. After it was washed with DCM (2 mL × 2), DMF (2 mL × 3) and DCM (2 mL × 3), the resin was dried under a vacuum for 3 h. The resin was treated with 95% TFA/H_2O for 1h and the filtrate was concentrated with Genevac evaporator.[17] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the crude product **8a**. (15.8 mg, 76%) ^{1}H NMR (Varian VXR-300S, 300 MHz, DMSO-d_6) δ 8.85 (d, J = 2.7 Hz, 1H), 8.57 (dd, J = 9.2, 2.7 Hz, 1H), 8.13 (dt, J = 8.7, 2.1 Hz, 2H), 7.72 (d, J = 9.2 Hz, 1H), 7.60 (dt, J = 8.7, 2.1 Hz, 2H), 4.28 (dt, J = 14.7, 6.3 Hz, 1H), 4.0 (dt, J = 14.7, 7.7 Hz, 1H), 1.80-1.71 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ESIMS m/z 390 $[M+H]^+$.
16. After the reduction of the nitro group of 7a, 4-[6-(benzoylamino)-2-oxido-4-oxo-1-propyl-1,4-dihydro-3*H*-2,1,3-benzothiadiazin-3-yl]benzoic acid was synthesized using benzoic acid anhydride.
17. Genevac HT-8 was available from Genevac Limited (Farthing Road, Ipswich, IP1 5AP, UK).