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# Efficient solid-phase synthesis of diverse 1,2,3-benzotriazin-4-ones using *tert*-butyl nitrite

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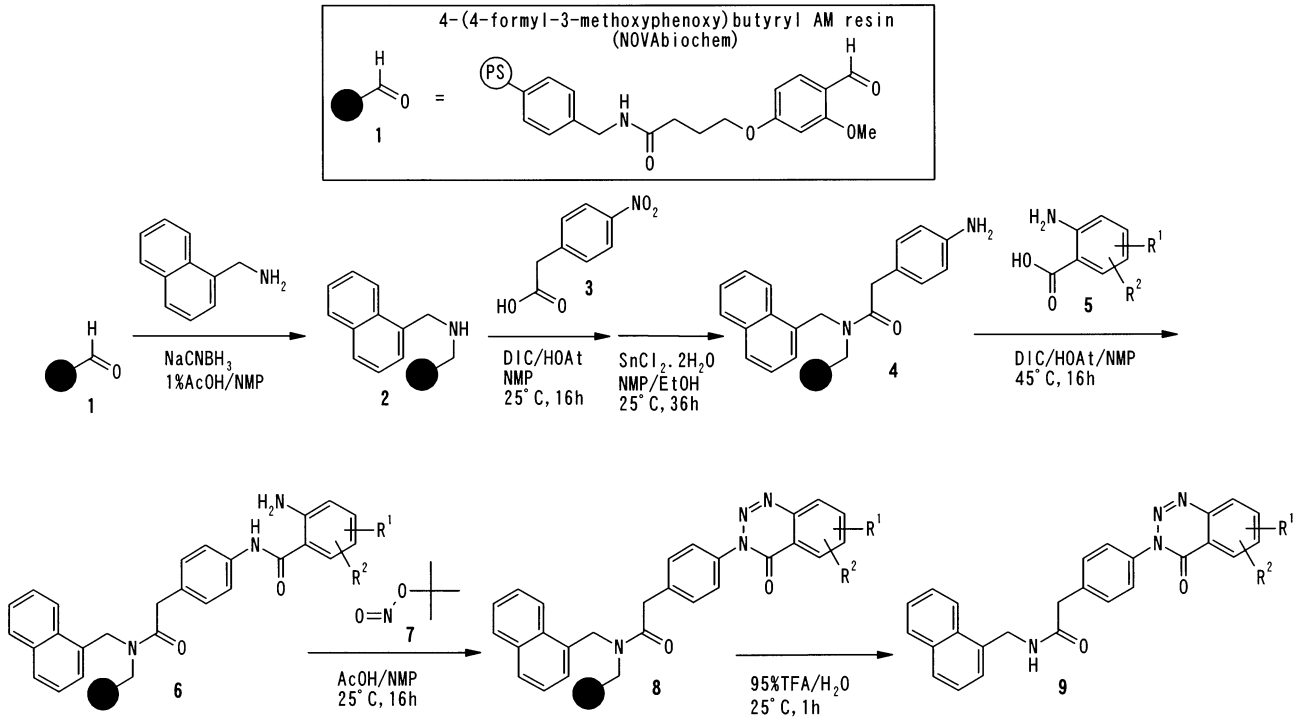
Solid-phase synthesis of small-sized, non-peptidic molecules has emerged as an important drug discovery tool.[1] Synthesis of heterocyclic compounds on solid-support, in particular, has been focused on because of their applications toward a variety of drug targets.[2] Among various heterocycles, quinazolines are especially attractive pharmacophores because of their wide range of pharmacological activities.[3] As a part of our project to develop an efficient synthetic protocol for quinazoline analogues from a resin-bound compound with a primary amine,[4] we investigated the synthesis of 1,2,3-benzotriazin-4-ones. 1,2,3-Benzotriazin-4-ones are pharmaceutically interesting as they show various biological activities such as sedative,[5] diuretic,[6] anesthetic[7] and antiarthritic[8] activities. Furthermore, the replacement of the pteridyl moiety of folic acid with 1,2,3-benzotriazin-4-ones was achieved, maintaining antitumor activity.[9] Therefore, the development of solid-phase




**Scheme 1.** Solid-phase synthesis of 1,2,3-benzotriazin-4-ones using various 2-aminobenzoic acids.

*Abbreviations: N,N′*-diisopropylcarbodiimide (DIC); 1-hydroxy-7-azabenzotriazole (HOAt); dichloromethane (DCM); dimethylformamide (DMF); *N*-methylpyrrolidone (NMP); trifluoroacetic acid (TFA).

*Keywords*: solid-phase synthesis; 1,2,3-benzotriazin-4-ones; drug; diazotization.

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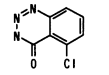
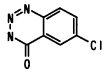
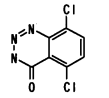
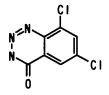
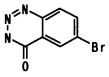
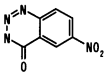
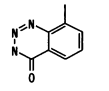
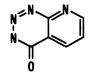
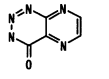
synthesis for 1,2,3-benzotriazin-4-ones was important from the viewpoint of drug discovery.

Resin-bound aniline **4** in Scheme 1 was prepared according to a previous report.[4f] 2-Aminobenzamides **6** was initially prepared via coupling of **4** with 2-nitrobenzoic acids and subsequent reduction of the nitro group. Although this synthetic method appeared to be useful thanks to the wide range of commercially available 2-nitrobenzoic acids, we found that only a limited number of 2-nitrobenzoic acids worked with this chemistry due to the generation of by-products during the reduction of the nitro group (data not shown). To avoid the reduction of the nitro group, 2-aminobenzoic acids were coupled without protecting the amines, successfully giving 2-aminobenzamides **6** with high purity owing to the low nucleophilicity of the amines. Because a number of 2-aminobenzoic acids were also commercially available, preparation of variety of 2-aminobenzamides **6** was possible.

Next, cyclization of **6** through diazotization was attempted using $NaNO_2$. Although this diazotization in solution-phase synthesis has been achieved with highly acidic solvents such as TFA[10] or aqueous HCl,[11] the treatment of **6** with these acids caused the cleavage of the compounds. Thus, we investigated the diazotization under milder acidic conditions, finding the treatment of **6** with $NaNO_2$/AcOH/$H_2O$ gave **8**. Nevertheless, the handling of the reaction was difficult due to the generation of gas during the reaction, because we prefer to use sealed vessels to carry out solid-phase reactions. Therefore, we examined various reaction conditions using different reagents, finding the treatment of **6** with *tert*-butyl nitrite/AcOH gave **8** without generating gas during the reaction. *tert*-Butyl nitrite and isoamyl nitrite were previously used for the preparation of triadine linkers[12] and the synthesis of benzotriazoles[13], respectively, with acids such as $BF_3$.[14] After the treatment of the resins with 95% TFA/$H_2O$, 1,2,3-benzotriazin-4-ones with a variety of substituents were successfully obtained in high purity (**9a**–**g**) as shown in Table 1.[15] 2-Aminobenzamides **6** with the aromatic nitrogen atoms gave 2-pyridinones in Figure 1 instead of the target compounds (**9h**–**i**). These by-products were probably generated by the additional reaction of **9h**–**i** with $H_2O$ under the cleavage condition.[16]

Furthermore, 1,2,3-benzotriazin-4-ones **13** were derivatized from various resin-bound anilines **12** (Scheme 2). As shown in Table 2, 1,2,3-benzotriazin-4-ones **13** were obtained with good to excellent purity, showing the feasibility of this solid-phase synthesis.[17] All the structures in this manuscript were confirmed by $^1H$ NMR and ESI mass spectrometer.

**Table 1.** Solid-phase synthesis of 1,2,3-benzotriazin-4-ones using various 2-aminobenzoic acids

| Entry | 9 | purity[a] (%) | yield[b] (%) |
|---|---|---|---|
| a |  | > 95 | 89 |
| b |  | 74 | 94 |
| c |  | 92 | 91 |
| d |  | > 95 | 85 |
| e |  | 85 | 80 |
| f |  | > 95 | 94 |
| g |  | 82 | 82 |
| h |  | 0 | – |
| i |  | 0 | – |

[a] Reverse-phase HPLC was carried out using rapid water (0.05% TFA)/acetonitrile (0.04% TFA) linear gradients from 5% organic to 98% organic component over 5 min. Flow: 1 mL/min. Column: Waters Symmetry C18 (3.5 μm) 2.1×30 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210+3*N*) nm, $N=0$–30.

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

In conclusion, the solid-phase synthesis of 1,2,3-benzotriazin-4-ones was achieved via cyclization of 2-aminobenzamides through diazotization using *tert*-butyl nitrite. Because this library contains three diversity-points, the preparation of a large number of compounds is possible with this solid-phase synthesis.

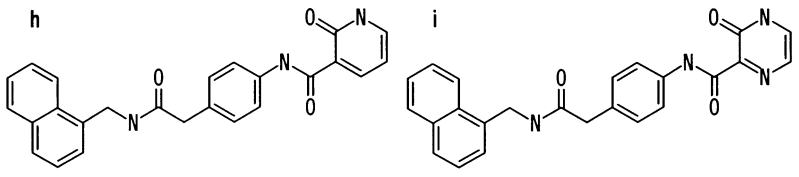
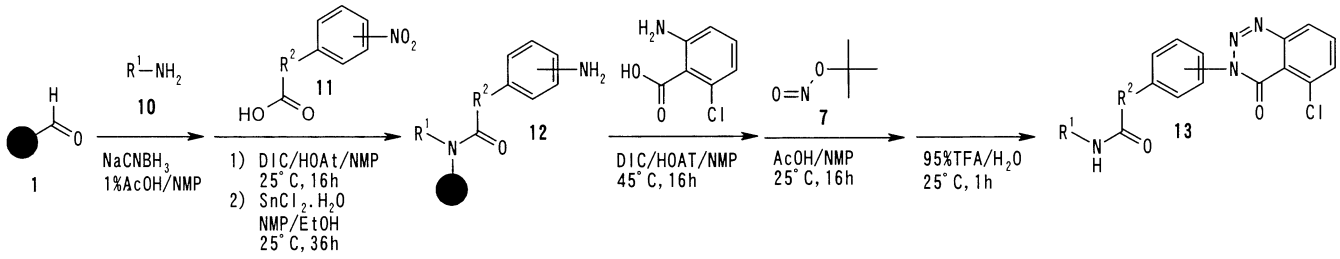
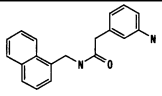
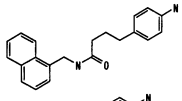
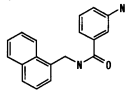
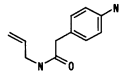
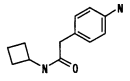
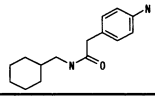



**Figure 1.** 2-Pyridinones obtained from 2-aminobenzamides **6** with the aromatic nitrogen atoms as by-products.




**Scheme 2.** Solid-phase synthesis of 1,2,3-benzotriazin-4-ones from variety of resin-bound anilines.

**Table 2.** Solid-phase synthesis of 1,2,3-benzotriazin-4-ones from variety of resin-bound anilines

| Entry | 13 | purity (%) | yield (%) |
|---|---|---|---|
| j |  | 94 | 92 |
| k |  | > 95 | 86 |
| l |  | 88 | 90 |
| m |  | > 95 | 95 |
| n |  | > 95 | 86 |
| o |  | > 95 | 92 |

In addition, the bioactivities of 1,2,3-benzotriazin-4-ones can be efficiently compared with other heterocycles, because the same resin-bound primary amines can also be derivatized into various heterocycles according to previous method.[4] This is especially useful for drug discovery processes in the pharmaceutical industry.

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14. Surprisingly, we found that diazotization of **6** proceeded sufficiently to give **8** without using any acids; however, the purity of the target compounds was slightly better using AcOH.
15. *General procedure for the preparation of* ***9a***: The resin-bound aniline **4** was prepared from 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin (NOVAbiochem, 100–200 mesh, loading 0.53 mmol/g, 60 mg) according to a previous report.[4f] The resin **4** was treated with 6-chloroanthranilic acid/DIC/HOAt/NMP (124 mg/56 μL/98 mg/2 mL) at 45°C for 16 h and washed with DMF (3×2 mL) and DCM (3×2 mL), and dried under vacuum for 3 h to give **6**. Then, the resin **6** was treated with *tert*-butyl nitrite/AcOH/NMP (50 μL/100 μL/1.4 mL) at 25°C for 16 h and washed with DMF (3×2 mL) and DCM (3×2 mL), and dried under vacuum for 3 h. The resin was treated with 95% TFA/$H_2O$ for 1 h and the filtered solution was concentrated. The residue was dis-

solved with 50% $CH_3CN/H_2O$ and lyophilized to give the product (**9a**, 12.8 mg) in 89% yield based on the theoretical loading weight of the target molecule. $^1H$ NMR (Varian VXR-300S, 300 MHz, DMSO-$d_6$) $\delta$ 3.60 (s, 2H), 4.75 (d, $J=5.4$ Hz, 2H), 7.44–7.56 (m, 8H), 7.82–7.87 (m, 1H), 7.91–8.06 (m, 4H), 8.19 (dd, $J=8.1$, 1.5 Hz, 1H), 8.67 (brt, $J=5.5$ Hz, 1H). MS $m/z$ 455, 457 $(M+1)^+$.

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17. It was also confirmed that this solid-phase synthesis worked with the resin-bound alkyl amine as follows: