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Short Report

Efficient Solid-phase Synthesis of 1,2,3-Benzotriazin-4-ones with SynPhase™ Lanterns

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A síntese de 1,2,3-benzotriazin-4-onas em fase sólida através da ciclização de 2-aminobenzamidas é descrita. O desenvolvimento de um método de síntese eficiente é importante para o desenvolvimento de drogas em razão da atividade biológica variada desses compostos. Os precursores de 1,2,3-benzotriazin-4-onas, as 2-aminobenzamidas, foram preparadas a partir de aminas ligadas a suporte sólido e ácidos 2-nitrobenzóicos. Várias 1,2,3-benzotriazin-4-onas foram obtidas em alta pureza utilizando-se SynPhase™ Lanterns."

We have developed a solid-phase synthesis of 1,2,3-benzotriazin-4-ones through cyclization of 2-aminobenzamides *via* diazotization. The development of an efficient synthesis is important from the viewpoint of drug discovery, considering the various bioactivities of these derivatives. The precursors of 1,2,3-benzotriazin-4-ones, 2-aminobenzamides, were prepared from solid-supported amines and 2-nitrobenzoic acids. Various 1,2,3-benzotriazin-4-ones were obtained with high purity using SynPhase™ Lanterns.

Keywords: solid-phase synthesis, drug, quinazoline, 1,2,3-benzotriazin-4-one, SynPhase™ Lantern, diazotization

Introduction

Solid-phase synthesis of small-sized, non-peptidic molecules has emerged as an important drug discovery tool.[1] The synthesis of heterocyclic compounds on solid-support, in particular, has been a focus of intensive study because of their applications toward a variety of drug targets.[2] Among various heterocycles, quinazolines are particularly attractive pharmacophores in view of their wide range of bioactivities.[3] As a part of our project to develop an efficient synthetic protocol for quinazoline analogues on solid-support,[4] we investigated the synthesis of 1,2,3-benzotriazin-4-ones. 1,2,3-Benzotriazin-4-ones have been known to possess various biological activities such as sedative,[5] diuretic,[6] anesthetic,[7] antiarthritic[8] and antitumor activity.[9] In addition, numerous heterocycles such as quinazoline-2, 4-diones,[4,10] 4-quinazolinones,[4,11] 2-thioxoquinazolin-4-ones,[4] 3-(sulfanyl)-1,2,4-benzothiadiazine 1,1-dioxide,[4] 1,2,4-benzothiadiazin-3-one 1,1-dioxides,[4] 2,1,3-benzothiadiazin-4-one 2-oxides,[4] benzimidazole,[12] hydantoin[13] and piperazinone[14] have been prepared from the solid-supported amines. Therefore, the bioactivities of 1,2,3-benzotriazin-4-ones and these heterocycles can be efficiently compared if appropriate synthetic methods are developed. Here, we report the first solid-phase synthesis of 1,2,3-benzotriazin-4-ones.

Results and Discussion

Wang-type SynPhase™ Lantern (**1a**)[15] bearing a 3-aminobenzoic acid ester[4] was reacted with 2-nitrobenzoyl chloride (**2a**)/2,6-lutidine to give **3a** (Scheme 1). The derivatized Lantern **3a** was treated with $SnCl_2 \bullet 2H_2O$/EtOH /NMP to give 2-aminobenzamide (**4a**) with high purity. Next, the cyclization of **4a** through diazotization was attempted. Diazotization of arylamines has been often performed with $NaNO_2$ in highly acidic solvents such as TFA[16] or concentrated HCl.[5] However, compounds on Wang-type solid-supports are cleaved off when treated with these solvents. Therefore, numerous solvents were tested for the diazotization and AcOH/H_2O (1/1) was found as the best solvent to give **6a** with high purity (Table 1). Other 1,2,3-benzotriazin-4-ones (**6b-d**) were also synthesized using the solid-supported arylamines and 2-nitrobenzoyl chloride. This synthetic method was found to work with a solid-supported alkylamine and phenylalanine ester (**6e**). 1,2,3-Benzotriazin-4-ones with substitutions on the aromatic ring were also synthesized using substituted 2-nitrobenzoic

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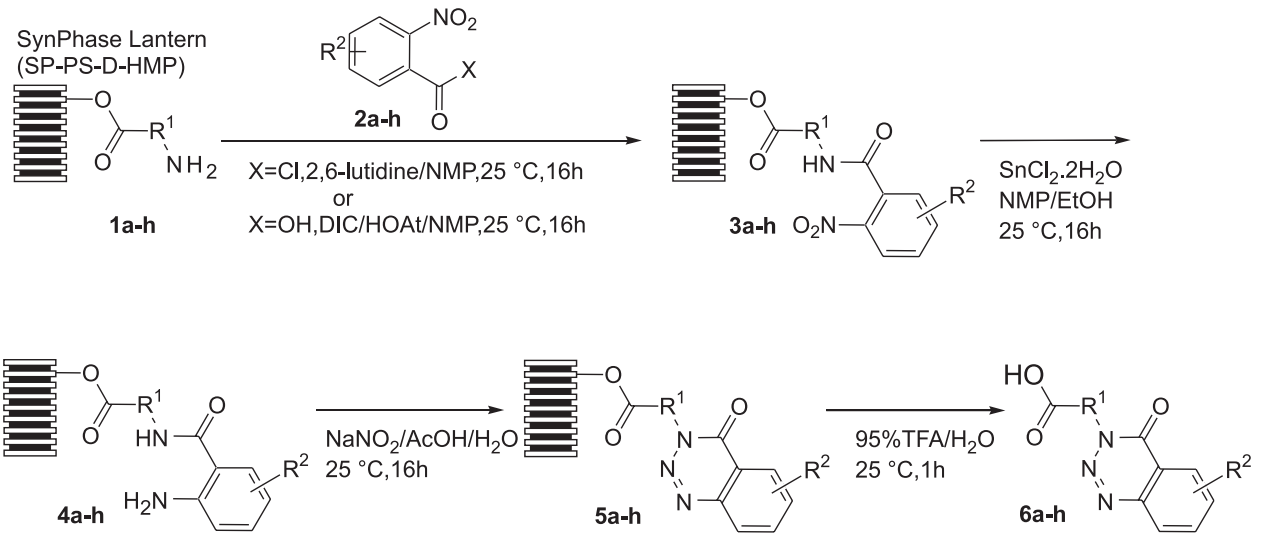


Scheme 1. Solid-phase synthesis of 1,2,3-benzotriazin-4-ones via diazotization of 2-aminobenzamides.

acids. 2-Nitrobenzoic acids were coupled with 3-aminobenzoic acid ester using N,N'-diisopropyl-carbodiimide (DIC)/1-hydroxy-7-azabenzotriazole (HOAt) to give **3f-h**. The usage of HOAt was important as the acylation was not completed with HOBt. Following a similar reaction sequence, substituted 1,2,3-benzotriazin-4-ones (**6f-h**) were successfully synthesized with high purity. Yields of products ranged from 46 - 83% based on the theoretical loading weights of the target molecules.[17] The structures of all the products in this manuscript were confirmed by ^{1}H NMR and LC-MAS (ESI mass spectrometry).

In conclusion, the solid-phase synthesis of 1,2,3-benzotriazin-4-ones has been accomplished by cyclization of 2-aminobenzamides via diazotization from various solid-supported amines and 2-nitrobenzoic acids. Although the size of the library is not large due to the limited diversity points (two diversity points), the same solid-supported amines can be derivatized into various heterocycles as described above, making this library an addition to the larger heterocycle library.

Experimental

General

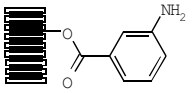
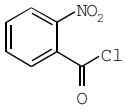
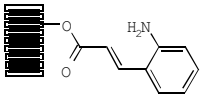
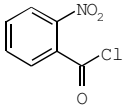
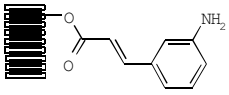
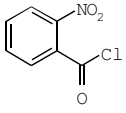
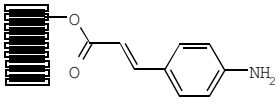
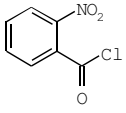
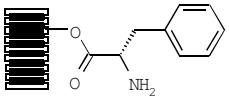
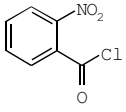
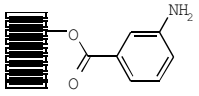
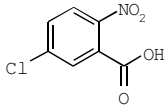
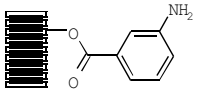
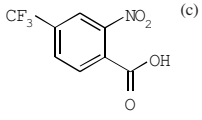
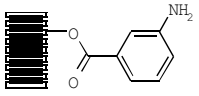
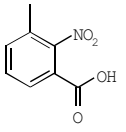
Commercial reagents were used without further purification. ^{1}H NMR spectra were recorded on Varian VXR-300S (300 MHz) spectrometers using tetramethylsilane as an internal standard. Liquid chromatography was performed using symmetry C_{18} column with ESI/PDA detection on Micromass platform.

*Representative procedure: synthesis of 3-(6-chloro-4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-benzoic acid (**6f**)*

SynPhase™ Lanterns bearing a 3-aminobenzoic acid ester (**1f**) were prepared according to the previous report.[4] The Lantern was treated with 5-chloro-2-nitrobenzoic acid /HOAt/DIC/NMP (1.0 mg/1.0mg/25 μL/2 mL) for 16 h at 60 °C to give **3f**. The Lanterns were washed with DMF (2 mL x 3) and CH_2Cl_2 (2 mL x 3) and dried under vacuum. After reduction of the nitro group with $SnCl_2 \bullet 2H_2O$/NMP/EtOH (1.0 g/2.0 mL/0.1 mL) for 16 h, the lantern was washed with DMF (2 mL x 3) and CH_2Cl_2 (2 mL x 3), and dried under vacuum for 1h to give **4f**. Acetic acid (1.0 mL) and H_2O (1.0 mL) were added to the Lantern in a 2.5 mL syringe with a cap[17], and immediately after adding solid $NaNO_2$ (100 mg), the syringe was sealed and put into a 50 mL Falcon tube[18] to prevent the syringe from opening. After shaking the tube for 16 h, the tube and the syringe cap were carefully removed and the lantern was washed with DMF (2 mL x 3) and CH_2Cl_2 (2 mL x 3) and dried under vacuum to give **5f**. The lantern was treated with 95% TFA/H_2O for 1 h and the solution was concentrated with a Genevac evaporater.[19] The residue was dissolved with 50% CH_3CN/H_2O and lyophilized to give the product **6f** (Entry f in Table 1) in 79% yield based on the theoretical loading weight of the target molecule.

*3-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-benzoic acid (**6a**).* ^{1}H NMR (DMSO-d_6) δ 7.73 (dd, 1H, *J* 7.8, 7.8 Hz), 7.94 (ddd, 1H, *J* 1.2, 2.4, 8.1 Hz), 7.7-8.03 (m, 1H), 8.08-8.18 (m, 2H), 8.24 (dd, 1H, *J* 1.7, 1.8 Hz), 8.28-8.36 (m, 2H). MS m/z 268 $(M + 1)^+$.

Table 1. Various 1,2,3-benzotriazin-4-ones (**6a-h**) synthesized according to Scheme 1. [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: 2 mL min^{-1}. Column: Waters Symmetry C_{18} (3.5 μm) 4.6 x 50 mm. HPLC purities were determined by summation of integrated HPLC peak areas at (210 + 3N) nm, N = 0 - 30. [b] Crude yields based on the theoretical loading weight of the target molecules. [c] Diazotization of 2-aminobenzamides was repeated 3 times to complete the reaction

Entry	1	2	6	
			purity (%)[a]	yield (%)[b]
a			> 95	76
b			> 95	66
c			> 95	64
d			> 95	46
e			> 95	83
f			92	79
g		 (c)	> 95	61
h			> 95	55

*3-[2-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-phenyl]-acrylic acid (***6b***).* ^{1}H NMR (DMSO-d_6) δ 6.61 (d, 1H, *J* 16.0 Hz), 7.67 (d, 1H, *J* 16.0 Hz), 7.62-7.73 (m, 2H), 7.84-7.89 (m, 1H), 7.98-8.04 (m, 2H), 8.13-8.19 (m, 1H), 8.29-8.36 (m, 2H). MS m/z 294 $(M + 1)^+$.

*3-[3-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-phenyl]-acrylic acid (***6c***).* ^{1}H NMR (DMSO-d_6) δ 6.59 (d, 1H, *J* 15.9 Hz), 7.22 (d, 1H, *J* 15.9 Hz), 7.64-7.69 (m, 3H), 8.01-8.10 (m, 2H), 8.18-8.23 (m, 1H), 8.34 (d, 1H, *J* 1.5 Hz), 8.37 (d, 1H, *J* 1.2 Hz). MS m/z 294 $(M + 1)^+$.

*3-[4-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-phenyl]-acrylic acid (***6d***).* ^{1}H NMR (DMSO-d_6) δ 6.65 (d, 1H, *J* 1.6 Hz), 7.69 (d, 1H, *J* 1.6 Hz), 7.72 (d, 2H, *J* 8.7 Hz), 7.92 (d, 2H, *J* 8.7 Hz), 7.98-8.03 (m, 1H), 8.13-8.19 (m, 1H), 8.28-8.29 (m, 1H), 8.31-8.36 (m, 1H). MS m/z 294 $(M + 1)^+$.

*2-(4-Oxo-4H-benzo[d][1,2,3]triazin-3-yl)-3-phenyl-propionic acid (***6e***).* ^{1}H NMR (DMSO-d_6) δ 3.53 (dd, 1H, *J* 11.0, 14.2 Hz), 3.65 (dd, 1H, *J* 5.1, 14.2 Hz), 7.08-7.16 (m,

5H), 7.91-7.96 (m, 1H), 8.07-8.13 (m, 1H), 8.17-8.23 (m, 2H). MS m/z 296 $(M + 1)^+$.

*3-(6-Chloro-4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-benzoic acid (***6f***).* ^{1}H NMR (DMSO-d_6) δ 7.72-7.77 (m, 1H), 7.91-7.95 (m, 1H), 8.09-8.12 (m, 1H), 8.18-8.25 (m, 2H), 8.31-8.36 (m, 2H). MS m/z 302, 603 $(M + 1)^+$.

*3-(4-Oxo-7-trifluoromethyl-4H-benzo[d][1,2,3]triazin-3-yl)-benzoic acid (***6g***).* ^{1}H NMR (DMSO-d_6) δ 7.76 (dd, 1H, *J* 7.8, 7.8 Hz), 7.95 (ddd, 1H, *J* 1.3, 2.2, 7.8 Hz), 8.12 (ddd, 1H, *J* 1.3, 1.4, 7.8 Hz), 8.26 (dd, 1H, *J* 2.2, 2.2 Hz), 8.30 (dd, 1H, *J* 1.4, 8.2 Hz), 8.53 (d, 1H, *J* 8.2 Hz), 8.73 (s, 1H). MS m/z 336 $(M + 1)^+$.

*3-(8-Methyl-4-oxo-4H-benzo[d][1,2,3]triazin-3-yl)-benzoic acid (***6h***).* ^{1}H NMR (DMSO-d_6) δ 7.73 (dd, 1H, *J* 7.8, 7.8 Hz), 7.87 (dd, 1H, *J* 7.8, 7.8 Hz), 7.92-7.95 (m, 1H), 7.96-8.01 (m, 1H), 8.07-8.11 (m, 1H), 8.17 (dd, 1H, *J* 0.9, 7.5 Hz), 8.23 (dd, 1H, *J* 1.8 Hz). MS m/z 282 $(M + 1)^+$.

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17. Disposable polypropylene / polyethylene syringes are available from Aldrich (Milwaukee, WI).
18. FALCON, BLUE MAXTM 50-ml polypropylene conical tube available from Becton Dickinson Labware (Franklin Lakes, NJ. USA 07417-1886).
19. Genevac HT-8 available from Genevac Limited (Farthing Road, Ipswich, IP1 5AP, UK).

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