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Solid-phase synthesis of functionalized 1,2,4-triazin-6-ones

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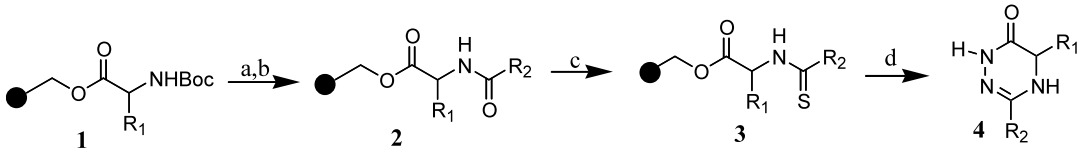
Abstract—The solid supported synthesis of functionalized 1,2,4-triazin-6-ones from resin bound amino acids and acid chlorides is described. A thioamide intermediate is generated with Lawesson's reagent, and the final products are cyclized and cleaved from resin with hydrazine. The products are obtained in good yield and purity. © 2002 Published by Elsevier Science Ltd.

Over the last decade, combinatorial chemistry has become an important tool in the drug discovery process. The synthesis of vast libraries of structurally diverse compounds based on heterocyclic scaffolds, including imidazoles, benzodiazepines, diketopiperazines, oxazolidinones, and quinolones have been disclosed.[1] Our efforts in this area have led to an investigation of the solid-phase synthesis of several types of heterocycles, including aminohydantoins,[2] 1,2,3-triazoles,[3] and 1,2,4-triazin-6-ones. As a class, 1,2,4-triazin-6-ones have been shown to posses a wide range of biological activity, including antibacterial, antifungal, antihypertensive, antiasthmatic, CCK antagonist, bronchodilatory, and lipoxygenase inhibition.[4] A brief examination of the literature revealed that the solid-phase preparation of this class of compounds had not yet been reported. We felt that the previously disclosed methods for the solution-phase synthesis[5] of this interesting class of compounds could be adapted to solid-phase synthesis for the preparation of screening libraries from commercially available resin bound amino acids and acid chlorides. Preparation of the critical thioamide on solid support, however, has not been reported, and the application of Lawesson's reagent to solid-phase synthesis has been limited.[6]

Commercially available Merrifield resin bound, Boc-protected amino acids (**1**) were readily converted to the requisite amide (**2**) by deprotection under standard conditions and condensation with an appropriate acid chloride. Conversion to the thioamide (**3**) was then accomplished by treating the resin with Lawesson's reagent in toluene at 75°C. Progress of the reaction can be easily monitored by IR, as the characteristic amide peak IR at 1675 cm^{-1} is lost as the reaction proceeds. The reaction conditions tolerate a wide range of solvents including 1,4-dioxane, acetonitrile, THF, dichloroethane, and 1,2-dimethoxyethane, allowing this procedure to be preformed in a variety of plastic vessels that are useful for the preparation of large combinatorial libraries. The solid by-products generated from the Lawesson's reagent, normally removed by filtration in a solution phase reaction, are easily eliminated by thorough washing of the resin with excess DMSO. Resin cleavage and cyclization with a 2% solution of hydra-



Scheme 1. Solid-phase synthesis of 1,2,4-triazin-6-ones. *Reagents and conditions*: (a) i. TFA, CH_2Cl_2, rt 1 h, ii. TEA, CH_2Cl_2, rt 1 h; (b) R^2COCl, DIPEA, CH_2Cl_2, rt 24 h; (c) Lawesson's reagent, toluene, 75°C, 5 h; (d) 2% hydrazine in isopropanol, 75°C, 24 h.

Keywords: solid-phase synthesis; 1,2,4-triazin-6-ones; Lawesson's reagent.
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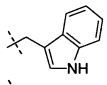
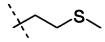
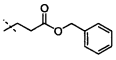
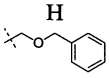
Table 1. Representative examples of the solid-phase synthesis of 1,2,4-triazin-6-ones[7]

Entry	R^1	R^2	Crude Yield (%)	HPLC Purity (%)[a]	Purified Yield[b]
1		Ph	75	95	55 %
2		2-Furyl	95	97	75%
3		2-Thiophenyl	100	88	69%
4		4-t-butyl-Ph	90	92	75%
5	Bn	Ph	75	98	70%
6	Bn	2-Furyl	88	95	72%
7	Bn	2-Thiophenyl	94	98	70%
8	Bn	4-t-butyl-Ph	75	96	68%
9	Me	Ph	90	94	53%
10		Ph	82	74	40%
11		Ph	79	94	45%
12		Ph	67	60	40%
13	H	Ph	35	89	23%
14		Ph	90	87	53%
15	i-Pr	Ph	63	96	58%

[a] HPLC purity was measured at 220 nm on a C18 symmetry column (4.6 x 50 mm; 5 μm) using a linear gradient from 100% water to 100% acetonitrile over 8 minutes (2.5 ml/ min flow rate).
[b] Yield based on initial loading.

zine in 2-propanol at 75°C for 24 h provides the desired 1,2,4-triazin-6-ones (**4**) in excellent yield and purity (Scheme 1 and Table 1). It should be noted that aliphatic acid chlorides failed to give the desired 1,2,4-triazin-6-one. While formation of the requisite thioamide was readily accomplished, cyclization did not occur under the condition described, and only the ring open product from hydrazine-mediated resin cleavage was obtained.

In summary, we have developed a method for the solid-phase synthesis of functionalized 1,2,4-triazin-6-ones. The products are obtained in good yield and the procedures are amenable to the production of combinatorial libraries.

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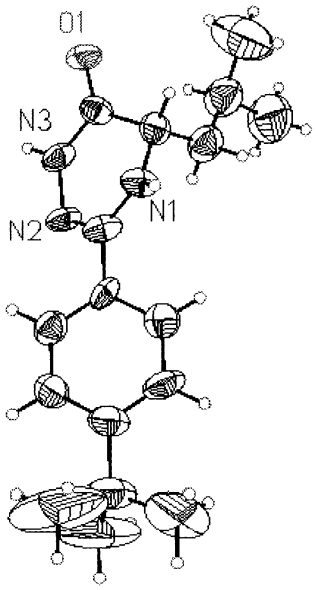
7. Representative procedure: Boc-protected phenylalanine Merrifield resin (5 g, loading 0.8 mmol/g) was treated with trifluoroacetic acid in methylene chloride (50%, 50 mL) for 2 h at rt. The resin was then filtered and washed successively with methylene chloride (three times), and methanol (three times). This was followed by neutralization of the salt with triethyl amine in methylene chloride (50%, 50 mL, 1 h). The resin was then filtered, washed as previously described, and dried under vacuum. 200 mg of the resin (0.16 mmol) was then placed in a 10 mL reaction vessel of a Quest™ 210. A solution of DIPEA (140 μL, 0.8 mmol), and *p-tert*-butyl benzoyl chloride (125 μL, 0.64 mmol) in 6 mL of methylene chloride was added, and the reaction was agitated overnight at rt. The vessel was drained and the resin washed as previously described, and dried under vacuum. The acylated resin (167.5 mg, 0.17 mmol) was



The X-ray crystal structure Table **1** Entry **4**
Thermal ellipsoids are plotted at 50% probability.

then suspended in 8 mL of toluene, 82.5 mg of Lawesson's reagent (0.20 mmol, 1.2 equiv.) was added, and the reaction was agitated at 75°C for 5 h. The reaction was cooled, the vessel was drained and the resin was washed successively with methylene chloride (3×6 mL), dimethyl sulfoxide (3×6 mL), and methanol (3×6 mL). The yellow resin was then dried under vacuum. The resin was then suspended in 8 mL of 2-propanol, and 160 μL of hydrazine was added. After agitating at 75°C for 24 h, the reaction was cooled, drained of solvent and washed with methylene chloride (three times), and methanol (three times). The solvent was collected and evaporated to yield the crude product. Purification by HPLC provided 34.9 mg (68%) of the desired product. Spectral data for Table 1: entry 1 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.03 (d, J=6.60 Hz, 6H), 1.60 (m, 2H), 1.94 (m, 1H), 4.05 (t, J=5.34 Hz, 1H), 7.45–7.70 (m, 5H). (M^+H) 232. Entry 2 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.00 (d, J=6.60 Hz, 6H), 1.55 (m, 2H), 1.90 (m, 1H), 4.00 (t, J=5.60 Hz, 1H), 6.57 (s, 1H), 6.90 (s, 1H), 7.65 (s, 1H). (M^+H) 222. Entry 3 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.03 (d, J=6.72 Hz, 6H), 1.59 (m, 2H), 2.10 (m, 1H), 4.02 (t, J=5.37 Hz, 1H), 7.12 (br s, 1H), 7.48 (d, J=4.86 Hz, 1H), 7.53 (d, J=6.12 Hz, 1H). (M^+H) 238. Entry 4 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.02 (d, J=6.60 Hz, 6H), 1.36 (s, 9H), 1.66 (m, 2H), 1.94 (m, 1H), 4.12 (t, J=5.40 Hz, 1H), 7.47–7.57 (m, 4H). (M^+H) 288. Entry 5 (^{1}H NMR, 300 MHz, CD_3OD): δ 3.15 (m, 2H), 4.42 (t, J=4.59 Hz, 1H), 7.29–7.60 (m, 10H). (M^+H) 266. Entry 6 (^{1}H NMR, 300 MHz, CD_3OD): δ 3.08 (m, 2H), 4.31 (t, J=4.59 Hz, 1H), 6.53 (s, 1H), 6.77 (s, 1H), 7.21 (br s, 5H), 7.61 (s, 1H). (M^+H) 256. Entry 7 (^{1}H NMR, 300 MHz, CD_3OD): δ 3.09 (m, 2H), 4.36 (t, J=4.93 Hz, 1H), 7.15 (br s, 1H), 7.31 (m, 5H), 7.42 (d, J=2.68 Hz, 1H), 7.56 (d, J=4.06 Hz, 1H). (M^+H) 272. Entry 8 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.34 (s, 9H), 3.04 (m, 2H), 4.36 (t, J=4.68 Hz, 1H), 7.23–7.45 (m, 9H). (M^+H) 322. Entry 9 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.43 (d, J=6.75 Hz, 3H), 4.13 (q, J=6.72 Hz, 1H), 7.42–7.50 (m, 5H). (M^+H) 190. Entry 10 (^{1}H NMR, 300 MHz, CD_3OD): δ 3.25 (m, 2H), 4.40 (t, J=4.46 Hz, 1H), 6.96–7.63 (m, 10H). (M+H) 305. Entry 11 (^{1}H NMR, 300 MHz, CD_3OD): δ 2.08 (m, 2H), 2.11 (s, 3H), 2.68 (t, J=5.22 Hz, 2H), 4.21 (t, J=5.73 Hz, 1H), 7.47–7.70 (m, 5H). (M^+H) 250. Entry 12 (^{1}H NMR, 300 MHz, CD_3OD): δ 2.18 (q, J=7.50 Hz, 2H), 2.62 (t, J=7.62 Hz, 2H), 4.21 (t, J=5.70 Hz, 1H), 5.11 (s, 2H), 7.33–7.73 (m, 10H). (M^+H) 338. Entry 13 (^{1}H NMR, 300 MHz, CD_3OD): δ 4.07 (s, 2H), 7.46–7.73 (m, 5H). (M^+H) 176. Entry 14 (^{1}H NMR, 300 MHz, CD_3OD): δ 3.80 (m, 2H), 4.20 (m, 1H), 4.55 (s, 2H), 7.23–7.62 (m, 10H). (M^+H) 296. Entry 15 (^{1}H NMR, 300 MHz, CD_3OD): δ 1.05 (dd, J=6.85 Hz each, 6H), 2.22 (m, 1H), 4.01 (d, J=4.08 Hz, 1H), 7.38–7.77 (m, 5H). (M^+H) 218.