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Solid-phase synthesis of 1-substituted 4,5-dihydro-1,2,4-triazin-6-ones

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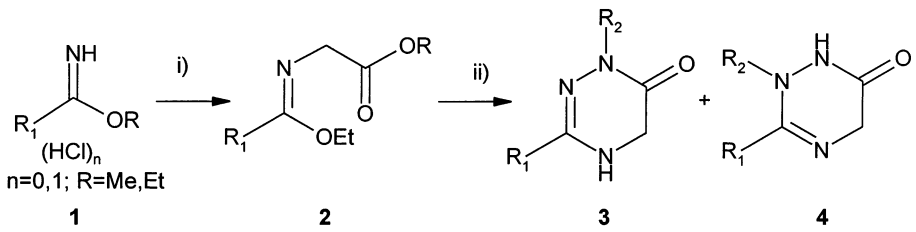
Abstract—The solid-phase synthesis of 1-substituted 4,5-dihydro-1,2,4-triazin-6-ones from imidate esters and substituted hydrazines is reported. The synthesis starts with the reaction of imidic esters with polymer-bound glycine to form the imidate esters. A rehearsal library of 59 compounds was synthesized.

1. Introduction

As part of a program to search for novel compounds with biological activity, we were interested in synthesizing a series of 1-substituted 4,5-dihydro-1,2,4-triazin-6-ones (**3**) with a variety of substituents in the 1- and 3-positions. Solution-phase based methodologies have already been developed,[1–5] but we decided to design a solid-phase synthesis route that would provide easier purification of intermediates and a higher throughput. No solid-phase synthesis of 4,5-dihydro-1,2,4-triazin-6-ones has been previously reported.

The reaction of an imidate ester with hydrazine is a known reaction for the preparation of 1-unsubstituted dihydro-1,2,4-triazin-6-ones.[2,3] The reaction of imidate esters **2** with substituted hydrazines to obtain dihydro-1,2,4-triazin-6-ones **3** has also been studied in solution phase (Scheme 1).[1,3–5] For example, 2,2,2-triethylhydrazine and pentafluorophenylhydrazine react with a glycine benzimidate to give the corresponding 4,5-dihydro-1,2,4-triazin-6-ones in 65 and 46% yields, respectively.[4] In the case of methylhydrazine (R_2 = Me), the reported product is a mixture of the two regioisomers **3** and **4**, with the desired isomer **3** as the minor component.[1,3,5] However, with other substituted hydrazines, the regioselectivity changed. No regioisomer **4** was found in the reactions of substituted benzimidates with 2,2,2-trifluoroethylhydrazine or with *m*-toluoylhydrazine.[1]



Scheme 1. Solution-phase synthesis and regioisomer of 1,2,4-dihydrotriazin-6-ones. *Reagents*: (i) Glycine hydrochloride, Et_3N, DCM:EtOH (95:5); (ii) R_2NHNH_2, EtOH.

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We wanted to have a methodology for the rapid analoguing of compound **3** that would overcome some of the difficulties that a parallel solution-phase chemistry would present. This paper reports the solid-phase synthesis of a set of diverse 4,5-dihydro-1,2,4-triazin-6-ones.

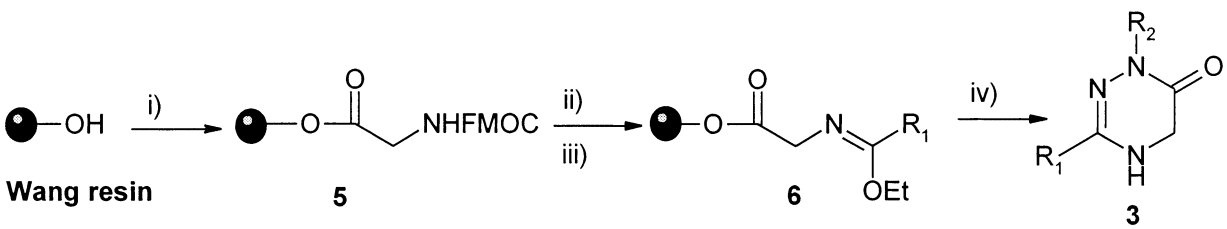
2. Results

The selection of starting materials was based on different factors such as commercial availability, previous analogues made in solution, molecular weight and diversity. A set of 33 imidic esters $\{R_1\}$ and 14 monosubstituted hydrazines $\{R_2\}$ was designed, giving a virtual library of 448 compounds **3{R$_1$,R$_2$}** (Table 1). A few imidic esters and imidic ester hydrochlorides are commercially available. The rest of the imidic esters **1** ($n=0, 1$) used for this study were prepared by the Pinner synthesis or by treatment of the corresponding nitrile with sodium methoxide.[6]

Attachment of FMOC–glycine to the Wang resin (Polymer Labs, 1.7 mmol/g) proceeded under standard DIPCDI coupling conditions (Scheme 2).[7,8] After 3 h, reaction in DMF still had 30% of unreacted Wang, while conversion was complete when the reaction was carried out in dichloromethane (DCM):DMF (5:1), as evidenced by MAS-NMR. Deprotection of the polymer-bound amino acid with 20% piperidine in DMF, followed by reaction with 2 equiv. of the corresponding imidic esters afforded intermediates **6**. The intermediate imidates are not stable to cleavage conditions and their structure was confirmed by photoacoustic FTIR (PAS-

Table 1. Selected imidic esters ($R_1C(NH)OEt$) and hydrazines (R_2NHNH_2)

No.	Imidic ester: **R$_1$**	No.	Imidic ester: **R$_1$**
1{1}	2,2,2-Trifluoroethoxypyridin-3-yl	**1{17}**	4-Ethoxyphenyl
1{2}	2,6-Dicholoropyridin-4-yl	**1{18}**	4-Ethylphenyl
1{3}	2-Furyl	**1{19}**	4-Fluorophenyl
1{4}	2-Naphthyl	**1{20}**	4′-Hexyloxybiphenyl-4-yl
1{5}	2-Pyridyl	**1{21}**	4-Methylphenyl
1{6}	3,4-Difluorophenyl	**1{22}**	4-Methylsulfanylphenyl
1{7}	3,5-Dibromo-4-methoxyphenyl	**1{23}**	4′-Nitrobiphenyl-4-yl
1{8}	3-Methoxyphenyl	**1{24}**	4-Phenoxyphenyl
1{9}	3-Methyl-4-nitrophenyl	**1{25}**	4-Propoxyphenyl
1{10}	3-Methylphenyl	**1{26}**	4-Trifluoromethylphenyl
1{11}	3-Nitrophenyl	**1{27}**	6-Methoxypyridin-3-yl
1{12}	3-Trifluoromethylphenyl	**1{28}**	*N*,*N*-Dimethylaminophenyl
1{13}	4-[1,2,3]Thiadiazol-4-ylphenyl	**1{29}**	Methyl
1{14}	4-Biphenyl	**1{30}**	Pyrazin-2-yl
1{15}	4-Butoxyphenyl	**1{31}**	Quinolin-3-yl
1{16}	4-Chlorophenyl	**1{32}**	Trifluoromethyl
No.	Hydrazine: **R$_2$**	No.	Hydrazine: **R$_2$**
{1}	2,2,2-Trifluoroethyl	**{8}**	Benzyl
{2}	2-Cyanoethyl	**{9}**	Butyl
{3}	2-Phenylethyl	**{10}**	Ethyl
{4}	3-Methylphenyl	**{11}**	H
{5}	4-Chlorophenyl	**{12}**	Methoxycarbonylmethyl
{6}	4,5-Dihydro-1*H*-imidazol-2-yl	**{13}**	Methyl
{7}	Benzothiazol-2-yl	**{14}**	Propyl



Scheme 2. Solid-phase synthesis of 1-substituted 4,5-dihydro-1,2,4-triazin-6-ones. *Reagents and conditions*: (i) FMOC–glycine, DIPCDI, DCM:DMF (5:1), rt, 3 h; (ii) 20% piperidine in DMF, rt, 30 min; (iii) **1**, Et_3N, DCM:EtOH (95:5), rt, 5 h; (iv) R_2NHNH_2, THF:EtOH (95:5), 50°C, 24–48 h.

FTIR) and MAS-NMR. As had been observed for the solution-phase synthesis[1] of these imidates, the addition of ethanol accelerates the reaction, while prolonged reaction times result in a reduction of the overall yield. For the imidic ester hydrochlorides 1 equiv. of Et_3N was added to the reaction, while for the free bases 1 equiv. of HCl (6 M in MeOH) was used.

Treatment of compounds **6** with hydrazines in HPLC grade THF:ethanol (95:5) at 50°C yields dihydrotriazinones **3** by a tandem cyclization cleavage reaction.

Contrary to the results reported in solution-phase chemistry, the reaction with methylhydrazine affords the desired regioisomer **3** as the major component of the reaction and compound **4** is not detected by NMR of the reaction mixture. This difference in reactivity might be caused by steric effects of the resin. The same result is observed for all the other hydrazines. Hydrazines **{6}** and **{7}** failed to give the desired targets, as did imidic esters **{28}** and **{32}**, the last ones probably due to the low stability of these molecules.

As noted previously, dihydrotriazinones are sensitive to oxidation to the corresponding 1,2,4-triazin-6-ones and/or the 1,2,4-dihydrotriazin-5,6-diones.[1,9,10] In general, some degradation during low-pressure column chromatography (Isco CombiFlash system on silica prepacked columns) was observed. Degradation products included the 1,2,4-triazin-6-ones, the 1,2,4-dihydrotriazin-5,6-diones and occasionally the amide R_1CONH_2.

From the virtual library of 448 analogues, 59 compounds were synthesized[11,12] in the first production batch. Yields after purification were moderate, ranging from 10 to 40%. Table 2 summarizes the set of compounds that was made; all compounds were analyzed by LC/MS[13] and showed purities >80%, in most cases >90% (UV at 220 nm).

In conclusion, we have developed a solid-phase synthesis of a diverse set of 1-substituted 4,5-dihydro-1,2,4-triazin-6-ones by reaction of polymer-bound imidate esters with substituted hydrazines, which allows the rapid analoging of the target molecules.

Table 2. Set of 1,2,4-dihydrotriazin-6-ones **3{R_1,R_2}**

No.	No.	No.	No.	No.
3{2,1}	**3{18,1}**	**3{16,2}**	**3{11,8}**	**3{4,11}**
3{3,1}	**3{19,1}**	**3{23,2}**	**3{2,9}**	**3{15,11}**
3{4,1}	**3{20,1}**	**3{18,3}**	**3{3,9}**	**3{3,12}**
3{6,1}	**3{22,1}**	**3{1,4}**	**3{4,9}**	**3{6,12}**
3{7,1}	**3{23,1}**	**3{13,4}**	**3{7,9}**	**3{10,12}**
3{9,1}	**3{25,1}**	**3{14,4}**	**3{8,9}**	**3{16,13}**
3{10,1}	**3{27,1}**	**3{22,4}**	**3{12,9}**	**3{24,13}**
3{11,1}	**3{30,1}**	**3{17,5}**	**3{17,9}**	**3{26,13}**
3{12,1}	**3{31,1}**	**3{20,5}**	**3{21,9}**	**3{15,14}**
3{13,1}	**3{6,2}**	**3{2,8}**	**3{24,9}**	**3{19,14}**
3{14,1}	**3{10,2}**	**3{5,8}**	**3{26,9}**	**3{30,14}**
3{15,1}	**3{15,2}**	**3{6,8}**	**3{27,10}**	

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11. Preparation of FMOC–gly–Wang resin: Wang resin (70 g, 119 mmol, PL-Wang, Polymer Labs, 1.7 mmol/g) was conditioned with DCM (550 ml) and DMF (100 ml) and stirred for 30 min. Then, FMOC–glycine (71 g, 238 mmol) was added, followed by diisopropylcarbodiimide (60 g, 476 mmol) and 4-dimethylaminopyridine (2.4 g, 19.7 mmol). The reaction was stirred for 3.5 h at room temperature, the resin was filtered, then washed in alternating MeOH and DCM and dried in a vacuum oven.
12. Preparation of the triazinone: FMOC–gly–Wang resin (1.3 g) was treated with piperidine (20% in DMF, 5 ml) for 20 min. The resin was filtered and washed with DMF, DCM and MeOH. Then, ethyl 4-phenyloxybenzimidate hydrochloride (874 mg, 3 mmol) was added as a solid, followed by 5 ml DCM and Et_3N (139 mg, 1.4 mmol in 2 ml methanol). The resin was shaken for 4 h at room temperature, filtered and washed in alternating DCM and MeOH. The resin was conditioned with DCM and butylhydrazine oxalate (532 mg, 3 mmol) was added, followed by Et_3N (581 mg, 6 mmol) and EtOH (1.5 ml). The reaction was shaken at 50°C for 48 h, the resin was filtered and washed with DCM. The evaporated crude was purified by low-pressure chromatography on silica to give 159 mg (33%) of **3{24,9}** as a yellow solid. LC/MS: 324 (M+H), 98%.
13. LC/MS analysis was conducted on a Hewlett–Packard HP1100 pump equipped with a Hewlett–Packard HP1050 variable UV detector set at 214 nm and a Metachem Polaris C-18, 50×3.0 mm, 3 μm column. The injection volume was 1 μl and the flow rate 0.8 ml/min of water:acetonitrile (0.1% acetic acid each) gradient. The mass spectrometer was a Micromass Quattro-SQ with a Fisons ESI source in a positive-ion detection mode.