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Efficient solid-phase synthesis of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones

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Abstract—A new and easy protocol for the formation of substituted 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones was developed on solid support. The heterocyclic compounds were formed by nucleophilic reaction of hydrazine on thioamide esters. As cyclization was concomitant with cleavage from the support, substituted 4,5-dihydrotriazinones were obtained in high purity.

Heterocyclic compounds are of great interest in modern medicinal chemistry. 4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones are heterocycles which can be considered as peptidomimetic structures of dipeptides or as potential templates for anchoring various pharmacophore groups in a privileged structure approach. Three different strategies have been formally applied for the preparation of 4,5-dihydrotriazinone derivatives. The first route was achieved by condensation of hydrazine, considered as a 1,2-dinucleophile on a 1,4-dielectrophile,[1–5] the second one concerned a cyclocondensation of an α-aminohydrazide (1,5-dinucleophile) onto an orthoester as 1,1-dielectrophile.[6] Recently, Saniere et al. reported the use of *N*-thioacylphtalimides as 1,1-dielectrophiles in a reaction with α-amino hydrazides to yield dihydrotriazinones.[7] As far as we know, no publication describes the solid-phase synthesis (SPS) of 4,5-dihydrotriazin-6-ones while the SPS of 3-amino-1,2,4-triazin-5(4*H*)-ones was reported once.[8] As part of our search into heterocyclic compounds[9] we decided to use a more practical approach to synthesize these molecules with the aim to generate quickly and easily libraries of compounds for lead compound research. To obtain a wide diversity and to apply this strategy to combinatorial chemistry, we needed to transfer this methodology to SPS. This was performed by hydrazine condensation on an α-(thioacyl)aminoester[5] linked to the solid support via its C-terminal carboxylic group and a hydrazine cyclization/cleavage step as shown in Scheme 1.

Hydroxymethyl polystyrene resin **1** (1.1 mmol/g) was converted into the corresponding *N*-protected α-aminoester **2** by activation of the carboxylic acid function with diisopropylcarbodiimide (DIC) in the presence of 4-dimethylaminopyridine (DMAP) as catalyst.[10] The unreacted hydroxymethyl groups were capped with Ac_2O in DCM, and after drying, an aliquot of the resin was used for loading determination by UV dosage of the Fmoc group release. The loading of the resin was in the range of 0.4 to 0.6 mmol/g depending of the *N*-protected α-aminoacid. After Fmoc deprotection of **2**, the amine was acylated with a selected carboxylic acid R_3-COOH (5 equiv.) using BOP[11] as coupling reagent in the presence of diisopropylethylamine (DIEA). The amide bond of **3** was then converted into thioamide on the solid support using Lawesson's reagent (LR) in refluxing THF as already described.[12,13] Three experiments were performed on a model dipeptidyl-resin with different quantities of LR (0.5, 1 and 3 equiv.) to optimize this reaction. At this stage, completion of the thionation reaction was necessary to avoid undesired formation of dipeptide hydrazide **6** during the hydrazine cleavage final step. Complete conversion of **3** into **4** was checked by cleavage of resin aliquots with TFA for these three experiments. Mass spectrometry and HPLC analysis of **4′** revealed that 3 equiv. of LR were needed. The reaction can also be conveniently monitored by IR analysis of the resin beads which show a disappearance of the amide carbonyl stretch at 1669 cm^{-1}. This thionation reaction on solid support was found very practical compared to solution synthesis. LR used in excess was eliminated by simple filtration in the case of SPS whereas the same reaction in solution needed a tedious

Keywords: Lawesson's reagent; 4,5-dihydrotriazin-6-one; thioamide; cyclocleavage.

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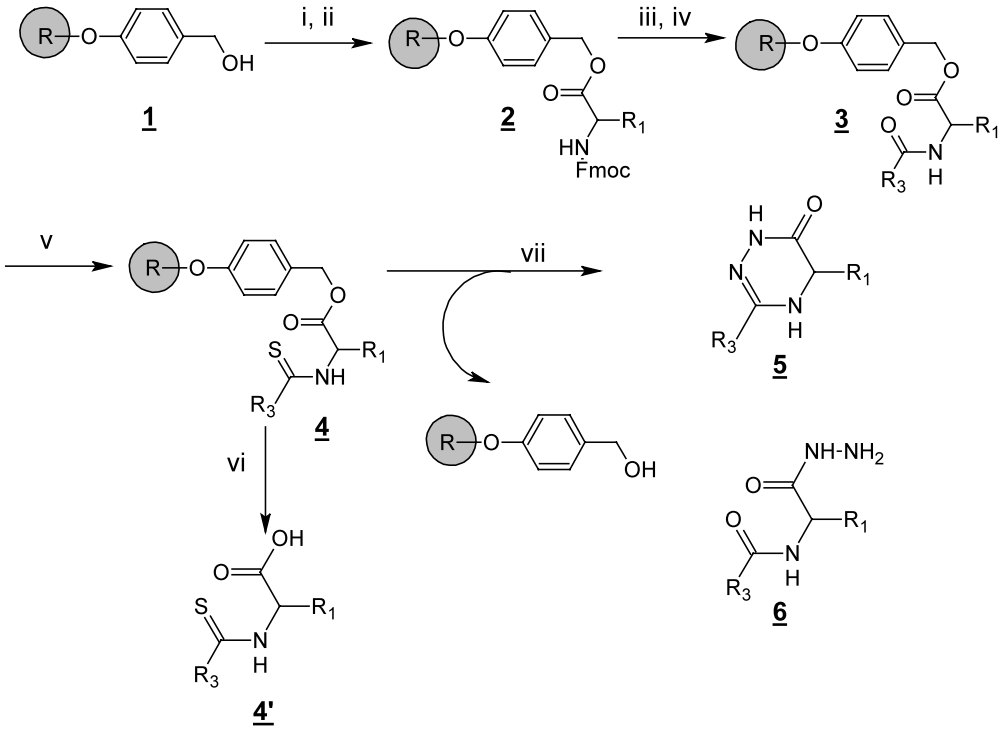

Scheme 1. Solid-phase synthesis of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones. *Reagents and conditions*: (i) 10 equiv. FmocAA_1OH, 5 equiv. DIC, DMAP cat.; (ii) Ac_2O/DCM 50/50 (v/v); (iii) DMF/Pip 80/20 (v/v); (iv) 5 equiv. R_3COOH, 5 equiv. BOP, 10 equiv. DIEA, DMF; (v) 3 equiv. LR, THF, 65°C, 3 h; (vi) TFA/TIS/H_2O 95/2.5/2.5 (v/v/v); (vii) 30 equiv. NH_2NH_2, H_2O, dioxane, 90°C, 16 h.

purification step. As the thionation reaction was performed at 65°C, it was specific to the amide bond and neither the ester nor the urethane reacted with LR even used in large excess.[14] The linked compound **4** was then placed in dioxane at 90°C in the presence of 30 equiv. of hydrazine hydrate for 16 h and the solutions containing the desired compounds **5** were then recovered after simple filtration. These crude samples were directly examined by HPLC to check their purity.

The following experimental procedure is representative of all synthesized compounds. 8.52 g of Fmoc-L-phenylalanine (22 mmol) was placed at 0°C in an ice bath and 0.5 equiv. of DIC (1.7 ml, 11 mmol) was added. After 30 min at this temperature, this mixture was added to 2 g of Wang resin (1.1 mmol/g) in a fritted SPS reactor. DMAP in a catalytic amount (0.14 g, 1.1 mmol) was added and the reaction was left overnight under mechanical stirring. After draining, the resin was sequentially washed twice with DMF, MeOH and DCM. The remaining hydroxyl groups were then capped with DCM/Ac_2O (50/50, v/v) for 30 min. After washings, the resin was dried in vacuo till constant weight. An aliquot of the resin was used for determination of the resin substitution by Fmoc release measurement followed by UV. A loading of 0.53 mmol/g was found. 300 mg of this resin (0.159 mmol) was placed in a reaction vessel on a Quest 210 organic synthesizer (Argonaut Technologies, San Carlos, CA). The temporary Fmoc group of the N-terminal function was removed by a 80/20 solution of piperidine/DMF for 5 then 15 min. After classical washings, *Z*-L-tryptophan (269 mg, 5 equiv., 0.79 mmol) and BOP (352 mg, 0.79 mmol) were added to the resin in 5 ml DMF, followed by 270 μl of DIEA (1.59 mmol). After 45 min of mechanical stirring, the reaction mixture was drained and the beads were washed twice with DMF and THF. LR (193 mg, 3 equiv., 0.48 mmol), then 5 ml of THF were added to the resin and placed under stirring at 65°C for 3 h. The reaction mixture was drained and the resin was sequentially washed with THF (2×) and dioxane (2×). 5 ml of dioxane and 222 μl of hydrazine hydrate (30 equiv., 4.77 mmol) were added to the reactor which was placed at 90°C under stirring for 16 h. The reactor was allowed to warm up to room temperature, the filtrate was recovered and the resin was washed with 5 ml dioxane which were combined with the previous ones. The crude mixture was dried under vacuum, dissolved in CH_3CN/H_2O (50/50, v/v) and lyophilized to yield a white foam which was analyzed. This procedure was applied concomitantly to all obtained compounds on the Quest apparatus. All compounds were characterized by HPLC and LC/MS (Fig. 1 and Table 1). As an example, physico-chemical data from compounds **f** and **g** are given.[15]

As this methodology was devoted to lead compound discovery, no special effort was done to avoid epimerization of the second introduced amino residue. Epimerization was detected by HPLC and LC/MS in the case of diastereomers (compounds **a**, **b**, **c**, **d** and **f**). Saniere et al.[7] reported that the use of mercury diac-

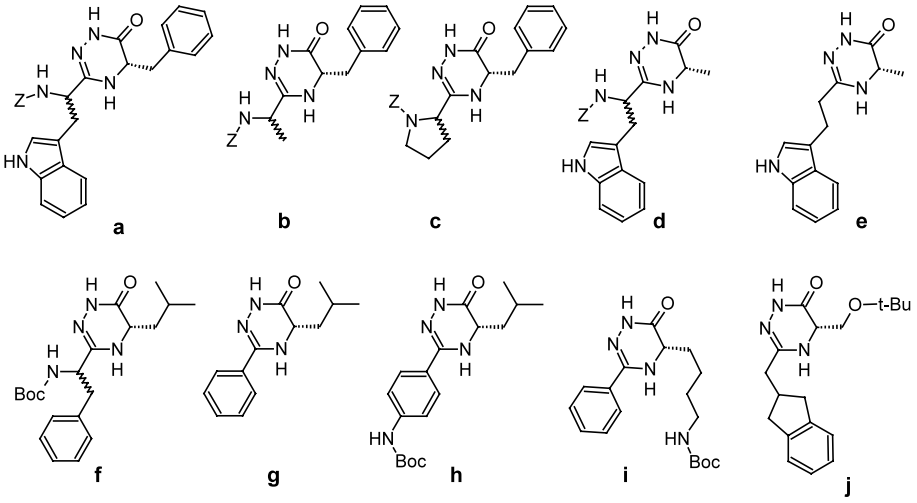

Figure 1. Synthesized molecules.

Table 1. Isolated yield, purity and physico-chemical characteristics of synthesized compounds

Compd	HPLC purity of crude product (%) at 214 nm/254 nm[a]	Isolated yield (%)[b]	Retention time t_R (min)[a]
a	83/86[c]	79	8.47
b	98/91[c]	75	6.88
c	95/100[c]	61	7.07
d	89/84[c]	80	7.20
e	68/64	60	4.30
f	75/58[c]	68	7.75 (maj.)/8.03 (min.)[d]
g	99/96	92	5.57
h	92/94	90	7.30
i	81/81	71	6.52
j	73/93	79	6.55

[a] Symmetry Shield Waters Column, C18, 5 μm, 150×3.9 mm; gradient from A to B in 15 min (A: H_2O, 0.1% TFA; B: CH_3CN, 0.1% TFA).
[b] Yields were calculated from the measured resin substitution and after flash purification.
[c] Both diastereoisomers were combined.
[d] Diastereoisomers were separated.

etate as a catalyst during the cyclization reaction under mild conditions resulted in practically no epimerization.

4,5-Dihydro-1,2,4-triazin-6(1*H*)-ones are interesting scaffolds as it is theoretically possible to introduce four different groups on the heterocycle as shown in Figure 2. Attempts for the cyclization/cleavage step with substituted hydrazines are under investigation in our laboratory ($R_4 \neq H$) and the alkylation of the amidine moiety is also under study ($R_2 \neq H$).

In conclusion, we described in this paper an easy, general and efficient solid-phase access to 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones. As aminoacids and carboxylic acids can be used as building blocks and as N_1 and N_4 sites are potential alkylation positions, generation of large libraries of compounds is possible. The products were obtained with good to excellent yields and with high purities.

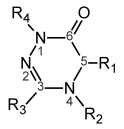

Figure 2. Further potential diversification of 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones.

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15. Compound **f**: $C_{20}H_{30}N_4O_3$; 374.48 g/mol; white foam; ^{1}H NMR of the major diastereoisomer (DMSO-d_6, 400 MHz, 300 K): δ 0.86 (6H, d, 6.6 Hz, 2×CH_3δLeu), 1.20–1.40 (11H, m, -C(CH_3)$_3$ Boc and CH_2βLeu), 1.72 (1H, m, CHγLeu), 2.82 (1H, dd, 13.4 Hz, 9.7 Hz, CH_2βPhe), 2.92 (1H, dd, 13.4 Hz, 5.6 Hz, CH_2βPhe), 3.78 (1H, m, CHαLeu), 4.21 (1H, m, CHαPhe), 6.86 (2H, m, NH urethane and NH amidine), 7.10–7.40 (5H, m, ar), 10.09 (1H, bs, NH amide); ^{13}C NMR of the major diastereomer (DMSO-d_6, 100 MHz, 300 K): δ 22.6 (CH_3), 2×23.9 (CH_3 and CH), 3×29.0 (3×CH_3), 39.3 (CH_2), 42.6 (CH_2), 51.4 (CH), 54.1 (CH), 78.9 ($C_{quat.}$), 2×127.1 (CH), 2×128.9 (CH), 130.0 (CH), 138.9 ($C_{quat.}$), 149.0 ($C_{quat.}$), 155.8 ($C_{quat.}$), 164.2 ($C_{quat.}$); MS (EI) m/z [M+H−56]$^+$ 319.3, [M+H]$^+$ 375.2, [2M+H]$^+$ 749.3.
Compound **g**: $C_{13}H_{17}N_3O$; 231.29 g/mol; colorless oil; ^{1}H NMR (DMSO-d_6, 400 MHz, 300 K): δ 0.92 (6H, d, 6.6 Hz, 2×CH_3δLeu), 1.42 (1H, m, CH_2βLeu), 1.44 (1H, m, CH_2βLeu), 1.85 (1H, m, CHγLeu), 3.85 (1H, m, CHαLeu), 7.35–7.50 (4H, m, NH amidine and 3H, ar), 7.70–7.80 (2H, m, ar), 10.40 (1H, bs, NH amide); ^{13}C NMR (DMSO-d_6, 100 MHz, 300 K): δ 23.0 (CH_3), 23.3 (CH_3), 23.8 (CH), 42.3 (CH_2), 51.6 (CH), 2×127.0 (CH), 2×129.2 (CH), 130.6 (CH), 133.4 ($C_{quat.}$), 145.5 ($C_{quat.}$), 164.6 ($C_{quat.}$); MS (EI) m/z [M+H]$^+$ 232.1.