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5-Substituted 4,5-Dihydro-1,2,4-triazin-3(2*H*)-ones from the Unprecedented Reaction between α-*N*-Protected Amino Acid Hydrazides and $NaBH_4$

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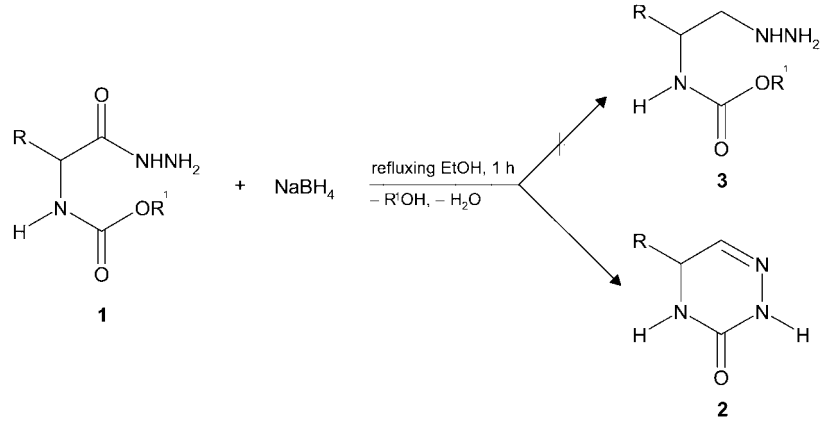
α-*N*-Protected amino acid hydrazides (**1**) readily reacted with $NaBH_4$ to afford 5-substituted 4,5-dihydro-1,2,4-triazin-3(2*H*)-one derivatives **2** in good yields. Unfortunately, the reaction caused partial racemization at the α-amino acidic carbon atom of the starting hydrazide. A mechanism, supported by experimental evidence, has been proposed in an attempt to explain this to date unprecedented reaction. The structure of compounds **2** was confirmed by X-ray structural analysis. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

Introduction

Combining our interest in some aspects of the chemistry of hydrazides[1] and our long-standing research into the use of $NaBH_4$,[2] we have investigated the reaction of a number of α-*N*-protected amino acid hydrazides (**1**) with the above reducing agent with the aim of obtaining the corresponding hydrazines (**3**, Scheme 1). Surprisingly enough, when an ethanolic solution of **1** was refluxed in the presence of $NaBH_4$ a six-membered heterocycle, namely 4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**2**), was almost exclusively formed



1	R	R^1	2	1	R	R^1	2
aa	$(CH_3)_2CH$	Et	**a**	**dc**	$PhCH_2$	$(CH_3)_3C$	**d**
ab	$(CH_3)_2CH$	$PhCH_2$	**a**	**ea**	$HOC_6H_4CH_2$	Et	**e**
ba	$(CH_3)_2CHCH_2$	Et	**b**	**fa**	$CH_3S(CH_2)_2$	Et	**f**
ca	Ph	Et	**c**	**ga**	(1*H*-indol-3-yl)CH_2	Et	**g**
da	$PhCH_2$	Et	**d**	**gc**	(1*H*-indol-3-yl)CH_2	$(CH_3)_3C$	**g**
db	$PhCH_2$	$PhCH_2$	**d**				

Scheme 1.

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(Scheme 1). To the best of our knowledge, there are a number of 4,5-dihydro-1,2,4-triazin-3-one ring systems described in the literature with substituents at the 6-position (**I**)[3] and one (**II**)[4] or two (**III**, **IV**)[5] at the 5-position (Figure 1).

Among the reported procedures suitable for obtaining compounds **I**–**IV**, the most efficient appear to be those

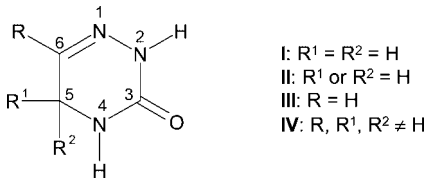


Figure 1. Chemical structures of derivatives **I**–**IV**.

involving the direct hydrogenation[4,5b] or, alternatively, the reduction with Grignard reagents[5a,5b,5d,5e] of the N4–C5 double bond present in a variety of 5- and/or 6-substituted 2,3-dihydro-3-oxo-1,2,4-triazines obtained from the condensation reaction between semicarbazide and the appropriate α,β-dicarbonyl compound. Surprisingly, the 5-substituted 4,5-dihydro-1,2,4-triazin-3-ones prepared by us, as well as our synthetic approach, do not appear to have any precedent in the chemical literature.

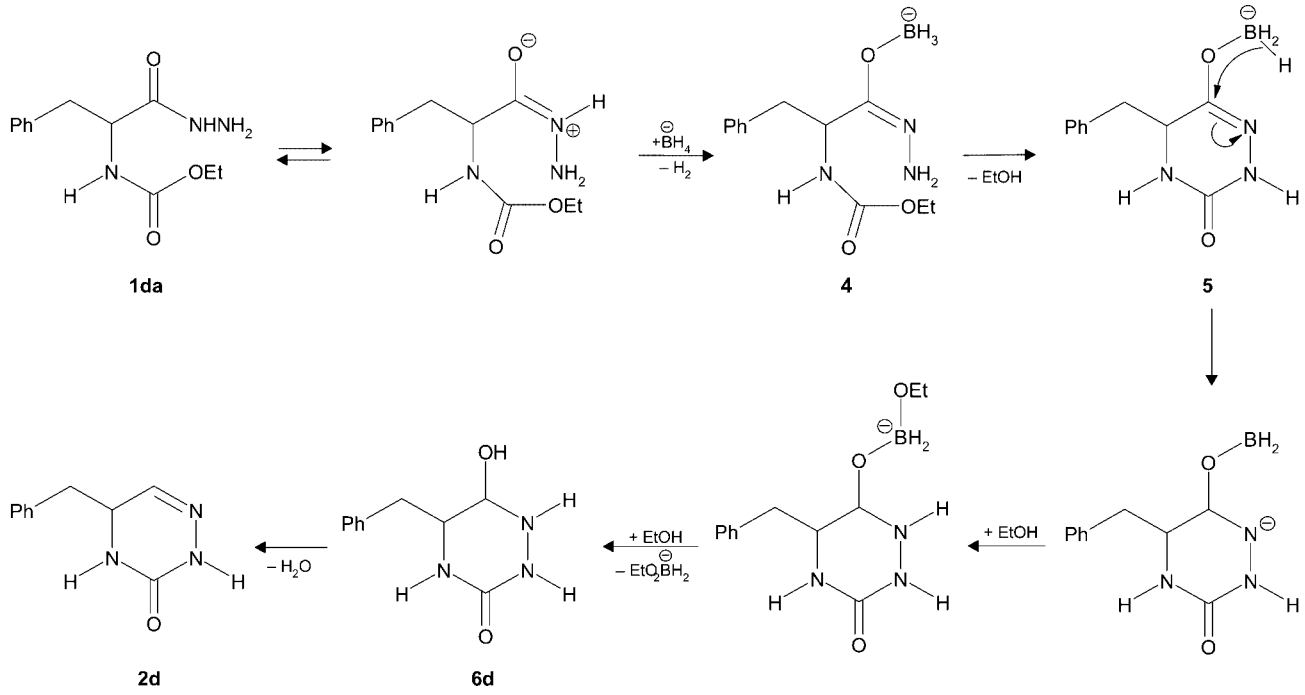
Results and Discussion

When an ethanolic solution of an α-*N*-protected amino acid hydrazide like **1** was refluxed in the presence of $NaBH_4$ a cyclization–reduction reaction took place to yield invariantly and almost exclusively 5-substituted 4,5-dihydro-1,2,4-triazin-3-one (**2**, Scheme 1).

Initially, we examined the reaction of the hydrazide of *N*-(ethoxycarbonyl)phenylalanine (**1da**) with 1.3 equiv. of $NaBH_4$ in refluxing EtOH. After 1 h, DI-MS analysis of the intact, carefully desolvented reaction mixture showed the presence of 5-benzyl-4,5-dihydro-1,2,4-triazin-3-one (**2d**) as the main component accompanied by the corresponding reduced product, namely 5-benzyl-1,4,5,6-tetrahydro-1,2,4-triazin-3(2*H*)-one.[6] Since the excess of $NaBH_4$ was considered responsible for the formation of 5-benzyl-1,4,5,6-tetrahydro-1,2,4-triazin-3(2*H*)-one, we repeated the reaction gradually decreasing the amount of the reducing agent employed, finally finding that 0.6 equiv. of $NaBH_4$ reduced the formation of the undesired side-product to a minimum while still allowing the complete conversion of **1da** into **2d**. Unfortunately, the reaction proceeded with unavoidable partial racemization (ca. 35%) at the α-amino acidic carbon atom of the starting hydrazide **1da**, as evidenced by HPLC analysis of **2d** carried out using a chiral column.

In order to rationalize this unprecedented reaction we suggest the mechanism outlined in Scheme 2. Hydrazide **1da** reacts with $NaBH_4$ to yield the intermediate **4** which, assuming the *anti* geometry favoured by steric hindrance, rapidly cyclizes to **5**. The reduction of **5** in the presence of EtOH produces the aminol **6d** and sodium diethoxydihydroborate. At this point, the unstable aminol **6d** affords 5-benzyl-4,5-dihydro-1,2,4-triazin-3-one (**2d**), whereas sodium diethoxydihydroborate, like $NaBH_4$, produces an additional molecule of **6d** and sodium tetraethoxyborate. Very likely the imine moiety present in **2d** is not reduced to an amine because the electrophilicity of the imine is decreased due to partial delocalization of the azomethine double bond.

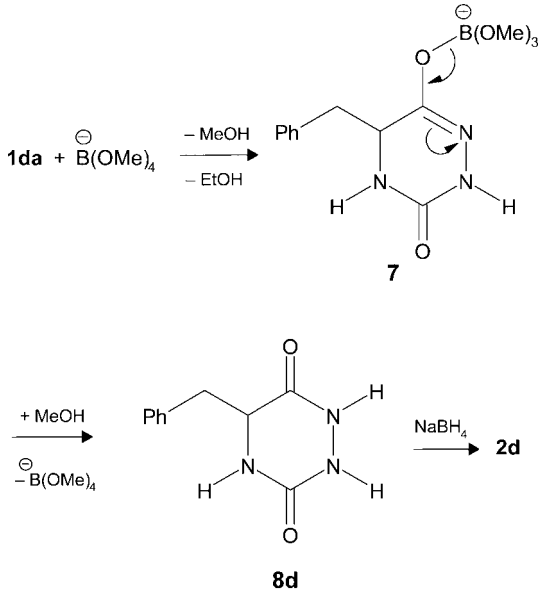
When the reaction was performed with 2-benzamido-3-phenylpropionohydrazide, a substrate that is unable to cyclize, we did not observe any reaction and 2-benzamido-3-phenylpropionohydrazide was recovered unchanged, even on forcing the reaction conditions (2.0 equiv. of $NaBH_4$, 3 h in refluxing EtOH). This fact is taken as a clear indication that the first step of the reaction was indeed the ring-closure of **3** to **5**. On the other hand, ring-closure did not occur at



Scheme 2.

all in the absence of $NaBH_4$, even on forcing the reaction conditions (1 d in refluxing EtOH), highlighting the fact that the presence of a species able to activate **1da** is essential.

Since **2d** was invariantly obtained with partial racemization, we investigated at which stage of the process the configurational damage occurred. With this aim, we attempted to prepare 5-benzyl-1,2,4-triazinan-3,6-one (**8d**) starting from **1da** and, taking into account the fact that $NaBH_4$ is essential for the cyclization reaction, we decided to utilize sodium tetramethoxyborate, which was able to react with **1da** like $NaBH_4$ (Scheme 3), but not to reduce the intermediate **7**.

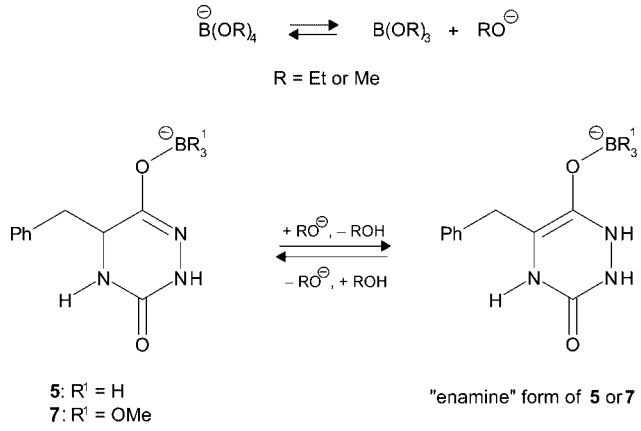


Scheme 3.

Sodium tetramethoxyborate was easily obtained by refluxing a solution of $NaBH_4$ (1.0 equiv.) in MeOH for 20 min.[7] The hydrazide **1da** (1.0 equiv.) was subsequently added to the solution thus obtained and the reaction mixture was refluxed for 1 h. After suitable work up, compound **8d** was successfully isolated in 90% yield, but partial racemization (ca. 35%) was evidenced, as shown by HPLC analysis under chiral conditions. Chiral HPLC, NMR and DI-MS analyses of the intact, carefully desolvented reaction mixture did not evidence the presence of 3-amino-5-benzylimidazolidine-2,4-dione, a product which might be formed during the cyclization of amino acid hydrazides in alkaline solution.

When **8d** was treated with $NaBH_4$ in refluxing EtOH, **2d** was obtained in 80% yield (Scheme 3) without affecting the *ee* initially present in **8d** (ca. 35%). These results, combined with the experimental evidence that 2-benzamido-3-phenylpropionohydrazide, which cannot undergo cyclization, was recovered without any detectable loss of optical purity after treatment with $NaBH_4$ in EtOH for 3 h at reflux, indicates that the racemization has to occur just after the cyclization step and not in the course of the subsequent reduction of **5** (Scheme 2) or **8d** (Scheme 3) to **2d**.

A possible species responsible for the observed racemization might be the alkoxy ion generated from the tetraalkoxyborate anion which favours the equilibration of **5** or **7** with the corresponding "enamine" form (Scheme 4).



Scheme 4.

In order to prevent, or at least reduce, the partial racemization that occurs during the formation of **8d**, compound **1da** was treated with sodium tetramethoxyborate, prepared as described above, at room temperature. After 2 h chiral HPLC analysis of the intact reaction mixture showed a low conversion of **1da** into **8d** (18%). The product **8d** was obtained as a mixture of the two enantiomers in an 8.5:1.5 ratio, whereas the unreacted **1da** was still detected as a single isomer, thus indicating that only the intermediates **5** or **7**, once formed, immediately undergo racemization. After complete conversion into **8d** (30 h), the observed isomerization was even worse (5.5:4.5 ratio). When the reaction of sodium tetramethoxyborate, prepared as described previously, with **1da** was carried out by replacing MeOH with THF or toluene, **8d** was invariably obtained with partial racemization, even at room temperature.[8]

Although the reaction was affected by unavoidable partial racemization, we decided to extend the cyclization–reduction procedure that produces **2** to other α-*N*-substituted amino acid hydrazides **1** (Scheme 1). We did not observe any significant difference in reactivity among the hydrazides **1** reported in Scheme 2, all affording the cyclic derivatives **2** in good yield within 1 h using 0.6 mol of $NaBH_4$ per mol of substrate in refluxing EtOH. Compounds **2** were obtained in an enantiomerically impure form, no matter which *N*-protecting group was present in the α-amino function and irrespective of the side-chain of the starting hydrazide **1**.

The presence of the triazinone ring in compounds **2** was confirmed unambiguously by X-ray diffraction analysis of 5-[(1*H*-indol-3-yl)methyl]-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**2g**). The resulting structure, shown in Figure 2, has the following features (see Figure 2 for atom numbering): (i) there are two enantiomers present and enantiomer B retains the configuration of the α-chiral centre at C3b of the starting hydrazide **1ga**; (ii) the triazinone ring is almost planar but with a small distortion, mainly in enantiomer B,

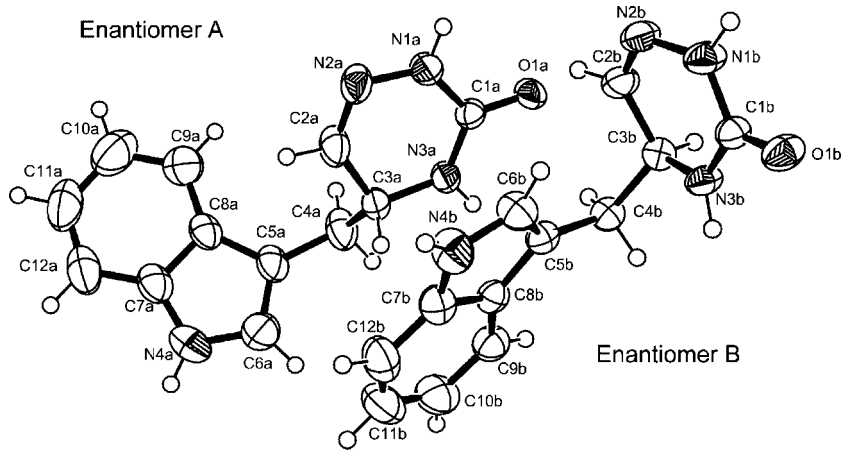


Figure 2. ORTEP view of the two enantiomers (A and B) of 5-[(1*H*-indol-3-yl)methyl]-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**2g**).

in the region that includes the sp^3-hybridized C3 atom (torsion angles N2–C2–C3–N3 and C1–N3–C3–C2 are –3.0 and 3.3°, respectively, in enantiomer A and 22.6 and –27.8°, respectively, in enantiomer B); (iii) the triazinone and the indole rings are almost orthogonal in enantiomer B (the torsion angles of N3b–C3b–C4b–C5b and C3b–C4b–C5b–C6b are 67.6 and 3.3°, respectively) whereas these two rings diverge in enantiomer A (the torsion angles of N3a–C3a–C4a–C5a and C3a–C4a–C5a–C6a are 175.0 and –82.4°, respectively).

X-ray diffraction analysis of 5-isopropyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**2a**) evidenced that this compound, which showed two peaks in the chiral HPLC analysis, crystallized to give a conglomerate; in fact, as shown in Figure 3, the crystal suitable for X-ray structural analysis contained only the enantiomer having the same configuration at C3 as the starting hydrazide **1aa**. Interestingly, the geometrical parameters of this enantiomer and enantiomer B of **2g** are similar even if the side-chains at C3 are rather different: (i) the almost planar triazinone ring shows a small distortion in the region that includes the sp^3-hybridized C3 atom (torsion angles N2–C2–C3–N3 and C1–N3–C3–C2 are –22.0 and 25.4°, respectively); (ii) the plane containing one of the two methyl groups (C6) of the isopropyl moiety is almost perpendicular to the triazinone ring (the N3–C3–C4–C6 torsion angle being 60.7°).

The ^{1}H NMR spectra of compounds **2** exhibit some common features due to the triazinone system: (i) a multiplet at δ = 3.8–4.3 ppm due to the 5-H atom; (ii) two broad singlets at δ = 5.3–7.0 and 7.7–9.6 ppm which correspond to the resonances of 4-H and 2-H, respectively, of the semicarbazide moiety (–C6H=N1–N2H–C3O–N4H–); (iii) an apparent triplet (J_{app} = 2.2–2.4 Hz) at δ = 6.6–6.8 ppm due to the resonance of the vinylic 6-H proton.

The multiplicity of this signal indicates a not unambiguous correlation of 6-H with another proton in addition to 5-H. Selective homonuclear ^{1}H–^{1}H decoupling experiments carried out with **2d** show that 6-H exhibits a coupling with 5-H ($^3J_{4\text{-H},5\text{-H}}$ = 2.7 Hz) and a long-range coupling with 4-H ($^4J_{4\text{-H},6\text{-H}}$ = 2.0 Hz). The ^{13}C NMR spectra of all the compounds **2** display a resonance due to the vinylic carbon at around δ = 140 ppm.

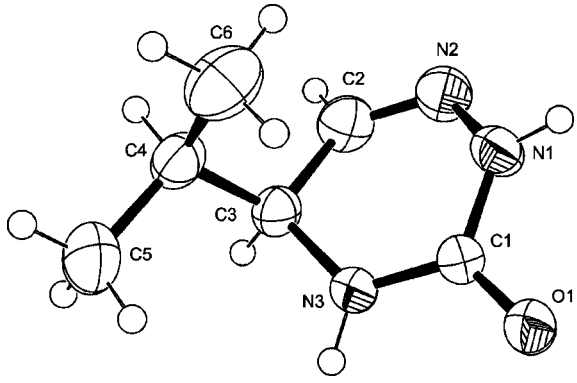


Figure 3. ORTEP view of 5-isopropyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (**2a**).

In conclusion, we have easily prepared a series of heterocyclic compounds, namely 4,5-dihydro-1,2,4-triazin-3-ones, with rigid frameworks containing natural amino acid moieties using an unprecedented synthetic approach. Unfortunately, the reaction proceeds with partial racemization at the α-chiral centre of the starting α-*N*-protected amino acid hydrazide.

Experimental Section

General Remarks: All reagents were of commercial quality (Aldrich, Fluka) and were used without further purification. The α-*N*-protected amino acid hydrazide **1** and 2-benzamido-3-phenylpropionohydrazide were prepared as described previously.[9] The reactions were monitored by high-performance liquid chromatography (HPLC) using a Waters M-45 apparatus on a Chiralcel OD column (250 × 4.6 mm, particle size 10 μm, detection at 254 nm and 2-propanol as the eluent (flow rate 0.3 mL/min). Direct-inlet mass spectra (DI-MS) were obtained with a Fisons TRIO 2000 gas chromatograph–mass spectrometer working in the positive-ion 70 eV electron-impact mode. Spectra were recorded in the range 35–450 a.m.u. Temperatures between 150 and 250 °C were found to be suitable to volatilize all the compounds into the ion source. IR

spectra were obtained with a Nicolet FT-IR Magna 550 spectrometer in the range 4000–400 cm^{-1} using the KBr technique for solids. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ and CD_3OD at room temperature or [D_6]DMSO at 40 °C as solvents. NMR peak locations are reported as δ values relative to TMS. Some ^1H multiplets are characterized by the term app (apparent): this refers only to their appearance and may be an oversimplification. Elemental analyses were performed with a Carlo Erba (Mod. 1106) elemental analyser. Melting points were determined with an automatic Mettler (Mod. FP61) melting-point apparatus and are uncorrected.

Synthesis of 5-Benzyl-1,2,4-triazinane-3,6-dione (8d): A solution of $NaBH_4$ (30 mg, 0.80 mmol) in MeOH (5 mL) was refluxed for 20 min. *N*-Ethoxycarbonylphenylalanine hydrazide (**1da**, 200 mg, 0.80 mmol) was subsequently added and the resulting reaction mixture was refluxed for 1 h. After evaporation of the solvent under reduced pressure, the residue was treated with 10% aqueous HCl (8 mL) and extracted with EtOAc (3×40 mL). The combined organic phases were washed twice with brine, dried with anhydrous Na_2SO_4, and filtered. Evaporation of EtOAc under reduced pressure afforded a residue consisting of a mixture of the two enantiomers of **8d** (148 mg, 90%) in a 6.5:3.5 ratio as evidenced by HPLC analysis using a chiral column. M.p. 208 °C (lit.:[10] 205–206 °C).

IR (KBr): $\tilde{\nu}$ = 3333, 3206, 3033, 2936, 1761, 1729, 1495, 1454, 1317, 975, 936, 920, 909, 762, 706, 622 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 2.89 and 3.00 (AB of ABX, 2 H, J_{AB} = 14.0, J_{AX} = 5.9, J_{BX} = 4.8 Hz, CH_2), 4.26–4.35 (m, 1 H, CH), 6.46 (br. s, 1 H, N*H*CONHNH), 7.13–7.37 (m, 6 H, Ar-H + NHCON*H*NH), 8.06 (br. s, 1 H, NHCONHN*H*) ppm. ^{13}C NMR ([D_6]DMSO): δ = 36.6, 55.6, 126.6, 128.0, 129.5, 135.6, 156.2, 171.5 ppm. MS (EI, 70 eV): *m*/*z* (%) = 205 (8) $[M]^+$, 177 (18), 120 (47), 114 (9), 91 (100), 77 (6), 65 (6). $C_{10}H_{11}N_3O_2$ (205.22): calcd. C 58.53, H 5.40, N 20.48; found C 58.48, H 5.44, N 20.43.

General Procedure for the Preparation of 5-Substituted 4,5-Dihydro-1,2,4-triazin-3(2*H*)ones 2a–g: A stirred mixture of the appropriate α-*N*-protected amino acid hydrazide (**1**, 1.80 mmol) and $NaBH_4$ (40 mg, 1.08 mmol) in absolute EtOH (10 mL) was refluxed for 1 h. After this time, EtOH was distilled off under reduced pressure, the residue was treated with 10% aqueous HCl (2 mL) and extracted with EtOAc (2×40 mL). The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the residue was triturated in hexane/Et_2O (1:1) to give **2a**–**g** as a mixture of two enantiomers, as evidenced by HPLC analysis using a chiral column.

5-Isopropyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2a): White solid (from **1aa**: 198 mg, 78%, two enantiomers in a 7.0:3.0 ratio; from **1ab**: 183 mg 72%, two enantiomers in a 6.8:3.2 ratio), m.p. 129 °C. IR (KBr): $\tilde{\nu}$ = 3236, 3109, 3084, 2961, 2910, 1698, 1474, 1347, 1299, 1164, 802, 763, 609, 528, 507 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.97 (d, J = 2.5 Hz, 3 H, CH_3), 1.01 (d, J = 2.5 Hz, 3 H, CH_3), 1.78–1.99 [m, 1 H, C*H*(CH_3)$_2$], 3.81–3.90 (m, 1 H, C*H*NH), 6.37 (br. s, 1 H, NHCO), 6.71 (app t, J = 2.4 Hz, 1 H, CH=N), 8.14 (br. s, 1 H, CONHN) ppm. ^{13}C NMR (CD_3OD): δ = 17.4, 17.8, 34.3, 58.1, 140.3, 154.9 ppm. MS (70 eV): *m*/*z* (%) = 141 (22) $[M]^+$, 126 (1), 99 (65), 98 (100), 70 (9), 56 (13), 43 (9). $C_6H_{11}N_3O$ (141.17): calcd. C 51.05, H 7.85, N 29.77; found C 51.01, H 7.80, N 29.80.

5-Isobutyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2b): White solid (262 mg, 94%, two enantiomers in a 7.3:2.7 ratio), m.p. 145 °C. IR (KBr): $\tilde{\nu}$ = 3236, 3109, 2961, 2921, 1704, 1654, 1474, 1347, 1296, 1164, 807, 766, 604, 528, 505 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.95 [app t, J = 6.7 Hz, 6 H, CH(CH_3)$_2$], 1.37–1.69 (m, 2 H, CH_2), 1.69–1.93 [m, 1 H, C*H*(CH_3)$_2$], 3.98–4.11 (m, 1 H, C*H*NH), 6.42 (br. s, 1 H, NHCO), 6.75 (app t, J = 2.2 Hz, 1 H, CH=N), 8.23 (br. s, 1 H, CONHN) ppm. ^{13}C NMR (CD_3OD): δ = 21.8, 22.8, 23.6, 42.5, 49.4, 140.1, 153.0 ppm. MS (70 eV): *m*/*z* (%) = 155 (14) $[M]^+$, 112 (3), 98 (100), 70 (6), 57 (2), 45 (22). $C_7H_{13}N_3O$ (155.20): calcd. C 54.17, H 8.44, N 27.07; found C 54.20, H 8.40, N 27.03.

5-Phenyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2c): White solid (284 mg, 90%, two enantiomers in a 6.7:3.3 ratio), m.p. 189 °C. IR (KBr): $\tilde{\nu}$ = 3231, 3104, 3073, 2905, 1698, 1648, 1541, 1485, 1459, 1301, 1154, 1021, 762, 700, 603, 583, 502 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 5.08 (br. s, 1 H, C*H*NH), 5.62 (br. s, 1 H, NHCO), 6.76 (br. s, 1 H, CH=N), 7.27–7.47 (m, 5 H, Ar-H), 7.90 (br. s, 1 H, CONHN) ppm. ^{13}C NMR (CD_3OD): δ = 56.6, 127.7, 129.5, 130.1, 139.8, 140.9, 154.1 ppm. MS (70 eV): *m*/*z* (%) = 175 (100) $[M]^+$, 174 (75), 147 (4), 146 (5), 131 (31), 105 (28), 104 (98), 103 (51), 98 (25), 78 (32), 77 (58), 51 (16). $C_9H_9N_3O$ (175.19): calcd. C 61.70, H 5.18, N 23.99; found C 61.75, H 5.20, N 23.95.

5-Benzyl-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2d): White solid (from **1da**: 323 mg, 95%, two enantiomers in a 6.5:3.5 ratio; from **1db**: 296 mg, 87%, two enantiomers in a 6.3:3.7 ratio; from **1dc**: 306 mg, 90%, two enantiomers in a 6.6:3.4 ratio), m.p. 134 °C. IR (KBr): $\tilde{\nu}$ = 3231, 3094, 1713, 1682, 1652, 1490, 1454, 1159, 743, 706, 586, 584 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.88 and 2.98 (AB of ABX, J_{AB} = 13.4, J_{AX} = 8.8, J_{BX} = 5.6 Hz, 2 H, CH_2), 4.16–4.28 (m, 1 H, C*H*NH), 5.38 (br. s, 1 H, NHCO), 6.78 (app t, J = 2.4 Hz, 1 H, CH=N), 7.15–7.43 (m, 5 H, Ar-H), 7.82 (br. s, 1 H, CONHN) ppm. ^{13}C NMR (CD_3OD): δ = 41.0, 53.6, 127.5, 129.5, 130.7, 137.0, 140.5, 154.5 ppm. MS (70 eV): *m*/*z* (%) = 189 (11) $[M]^+$, 115 (3), 98 (100), 91 (69), 77 (2), 70 (5), 65 (9). $C_{10}H_{11}N_3O$ (189.22): calcd. C 63.48, H 5.86, N 22.21; found C 63.51, H 5.84, N 22.18.

5-(4-Hydroxybenzyl)-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2e): White solid (277 mg, 75%, two enantiomers in a 6.7:3.3 ratio), m.p. 224 °C. IR (KBr): $\tilde{\nu}$ = 3292, 3216, 2814, 1719, 1678, 1596, 1525, 1476, 1448, 1377, 1331, 1250, 1198, 1174, 1149, 838, 807, 752, 713, 573 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 2.69 (app d, J = 5.9 Hz, 2 H, CH_2), 4.03–4.16 (m, 1 H, C*H*NH), 6.42 (br. s, NHCO), 6.58–6.79 (m, 3 H, CH=N + Ar-H), 6.95–7.08 (m, 2 H, Ar-H), 9.17 (br. s, 1 H, OH), 9.44 (br. s, 1 H, CONHN) ppm. ^{13}C NMR ([D_6]-DMSO): δ = 38.5, 51.8, 115.0, 126.2, 130.4, 138.5, 151.4, 155.9 ppm. MS (70 eV): *m*/*z* (%) = 205 (1) $[M]^+$, 107 (100), 99 (12), 98 (5), 70 (1). $C_{10}H_{11}N_3O_2$ (205.22): calcd. C 58.53, H 5.40, N 20.48; found C 58.50, H 5.44, N 20.52.

5-[2-(Methylthio)ethyl]-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2f): White solid (224 mg, 72%, two enantiomers in a 6.2:3.8 ratio), m.p. 104 °C. IR (KBr): $\tilde{\nu}$ = 3233, 3100, 2926, 1700, 1656, 1556, 1537, 1447, 1435, 1337, 1318, 1224, 776 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.93 (app q, J = 6.3 Hz, 2 H, CHC*H*$_2$), 2.11 (s, 3 H, SCH_3), 2.62 (t, J = 7.0 Hz, 2 H, SCH_2), 4.13–4.27 (m, 1 H, C*H*NH), 6.77 (app t, J = 2.2 Hz, 1 H, CH=N), 6.88 (br. s, 1 H, NHCO), 8.68 (br. s, 1 H, CONHN) ppm. ^{13}C NMR (CD_3OD): δ = 15.4, 29.1, 33.1, 50.4, 139.3, 153.3 ppm. MS (70 eV): *m*/*z* (%) = 173 (21) $[M]^+$, 125 (100), 112 (3), 98 (23), 75 (6), 70 (2), 61 (4), 47 (3). $C_6H_{11}N_3OS$ (173.23): calcd. C 41.60, H 6.40, N 24.26; found C 41.56, H 6.44, N 24.22.

5-[(1*H*-Indol-3-yl)methyl]-4,5-dihydro-1,2,4-triazin-3(2*H*)-one (2g): White solid (from **1ga**: 349 mg, 85%, two enantiomers in a 6.9:3.1 ratio; from **1gc**: 332 mg, 81%, two enantiomers in a 6.8:3.2 ratio), m.p. 185 °C. IR (KBr): $\tilde{\nu}$ = 3409, 3236, 3093, 1698, 1473, 1459, 1340, 1312, 746, 583, 512 cm^{-1}. ^1H NMR ([D_6]DMSO): δ = 2.95 (app d, J = 6.3 Hz, 2 H, CH_2), 4.13–4.24 (m, 1 H, C*H*NH), 6.70 (app t, J = 2.2 Hz, 1 H, CH=N), 6.90–7.24 (m, 4 H, Ar-H +

NHCO), 7.30–7.40 (m, 1 H, Ar-H), 7.50–7.59 (m, 1 H, Ar-H), 9.52 (s, 1 H, CONHN), 10.92 (br. s, 1 H, Ar-NH) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 21.9, 44.2, 100.7, 103.3, 110.2, 110.9, 113.4, 115.8, 119.7, 129.0, 132.5, 154.6 ppm. MS (70 eV): *m*/*z* (%) = 228 (1) [M]$^+$, 155 (1), 146 (1), 145 (1), 130 (100), 103 (3). $C_{12}H_{12}N_4O$ (228.25): calcd. C 63.15, H 5.30, N 24.55; found C 63.19, H 5.34, N 24.52.

Reaction of 5-Benzyl-1,2,4-triazinane-3,6-dione (8d) with NaBH$_4$: A stirred mixture of **8d** (120 mg, 0.58 mmol) and $NaBH_4$ (11 mg, 0.29 mmol) in absolute EtOH (3 mL) was refluxed for 1 h. After this time, EtOH was distilled off under reduced pressure, the residue was treated with 10% aqueous HCl (0.5 mL) and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with brine, dried with anhydrous Na_2SO_4 and filtered. After evaporation of the solvent under reduced pressure, the residue was triturated in hexane/Et_2O (1:1) to give **2d** (88 mg, 80%) as a mixture of two enantiomers in a 6.5:3.5 ratio, as evidenced by HPLC analysis using a chiral column.

X-ray Crystallography: Crystals of **2a** and **2g** were grown by slow evaporation from $CHCl_3$ solutions of the compounds. Structure solutions were obtained using SHELXS-86[11] and refined with SHELXL-97[12] using the full-matrix least-squares method. X-ray crystallographic data for **2a** and **2g** were collected at 298 K with a Bruker-Axs three circle diffractometer equipped with a Smart-Apex CCD detector using graphite-monochromated Mo-K_α radiation (λ = 0.7107 Å).

Crystallographic Data for 2a: 5802 reflections were obtained up to 2θ = 60.4° from a monoclinic crystal [molecular formula $C_6H_{11}N_3O$, space group $P\bar{1}$, a = 5.427(1), b = 7.131(1), c = 10.607(1) Å, α = 97.919(3), β = 92.811(3), γ = 110.19(3)°, V = 379.53 Å^3, Z = 2, D = 1.24 g/cm^{-3}, linear absorption coefficient 0.088 mm^{-1}] of dimension 0.40 × 0.30 × 0.10 mm. Unit-cell dimensions were calculated from least-squares refinement of the *d* values obtained from reflections in the θ range 2–12°. The number of unique reflections used to solve and refine the crystal structure was 2192 (R = 0.057). The non-hydrogen atoms were refined anisotropically; the hydrogen atoms were placed in calculated positions and refined as riding atoms. The final value of R for the observed reflections was 0.068 and the value of R for the whole data set was 0.106 (wR = 0.169, goodness of fit = 1.077, parameters/F_o ratio = 17.29). The absolute structure was fixed by comparison with a known structure.

Crystallographic Data for 2g: 17595 reflections were obtained up to 2θ = 30.0° from a monoclinic crystal [molecular formula $C_{12}H_{12}N_4O$, space group $P2_1$, a = 7.078(4), b = 8.695(5), c = 18.492(7) Å, β = 96.881(4)°, V = 1129.86 Å^3, Z = 2, D = 1.34 g/cm^{-3}, linear absorption coefficient 0.091 mm^{-1}] of dimension 0.36 × 0.30 × 0.15 mm. Unit-cell dimensions were calculated from least-squares refinement of the *d* values obtained from reflections in the θ range 2–12°. The number of unique reflections used to solve and refine the crystal structure was 6589 (R = 0.032). The non-hydrogen atoms were refined anisotropically; the hydrogen atoms were placed in calculated positions and refined as riding atoms. The final value of R for the observed reflections was 0.059 and the value of R for the whole data set was 0.083 (wR = 0.139, goodness of fit = 1.083, parameters/F_o ratio = 16.51). The absolute structure was fixed by comparison with a known structure.

CCDC-293341 (for **2a**) and -293338 (for **2g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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