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Diastereoselective synthesis of 3-substituted acylamino-3,4-dihydro-1,2,4-triazinones

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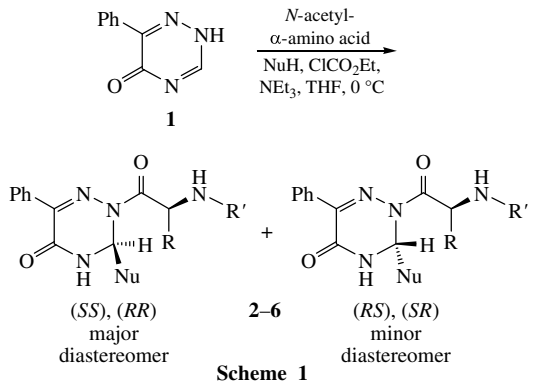
6-Phenyl-1,2,4-triazin-5(4*H*)-one **1** reacts with C-nucleophiles, such as indole, in the presence of *N*-acetylamino acids, to yield 2-acyl-3-indolyl-6-phenyl-3,4-dihydro-1,2,4-triazin-5(4*H*)-ones **2**–**6** with high diastereoselectivity.

In the presence of optically active acylation reagents, the addition of C-nucleophiles to a prochiral C=N double bond in azines results in the formation of addition products with high diastereoselectivity.[1,2] Comins[2] found the asymmetric induction in the reactions of nucleophiles to 4-methoxypyridines, which are acylated by chiral chloroformates. Such reactions are useful in the synthesis of alkaloid structures.[1,2] Amino acid fluorides can also be used as chiral auxiliaries in reactions of this type.[3–5] We reported previously that 3-aryl-1,2,4-triazin-5(4*H*)-ones can give asymmetric products with high diastereoselectivity in reactions with C-nucleophiles in the presence of DCC-activated amino acids.[6]

6-Phenyl-1,2,4-triazin-5(4*H*)-one **1** was acylated by N-substituted L-amino acids in the presence of ethyl chloroformate and reacted with C-nucleophiles yielding 3-substituted 2-(2-acylamino)acyl-6-aryl-3,4-dihydro-1,2,4-triazin-5(4*H*)-ones **2**–**6** in moderate yields but with high diastereoselectivity (Scheme 1, Table 1).[†,‡]



Scheme 1

In attempts to optimise the synthesis of compounds **2**–**6**, reaction conditions were varied for valine-derived product **3**. We observed that the replacement of a THF solvent by acetonitrile or dichloromethane and the use of a higher dilution decreased the yield. Changing the ratio of reactants and the reaction temperature did not increase the yield.

The ^{1}H NMR analysis of compounds **2**–**6** indicates the formation of only one pair of diastereomers in each case. In order to determine the relative stereochemistry, the X-ray analysis of compounds **3** and **6** was performed (Figures 1 and 2).[§] The analysis established that the compounds represent a pair of *SS*- and *RR*-enantiomers.

Table 1 Reactions of triazinone **1** with amino acids.

Nucleophile NuH	*N*-acetyl-α-amino acid	Product[a]	Yield (%)
Indole	*N*-Acetyl-L-leucine	**2**	49
Indole	*N*-Acetyl-L-valine	**3**	76
1-Methylindole	*N*-Acetyl-L-valine	**4**	40
Indole	*N*-Acetyl-L-tryptophane	**5**	32
Pyrrole	*N*-Acetyl-L-valine	**6**	30

[a]Diastereomeric ratio > 95:5 for products **2**–**6** (from ^{1}H NMR).

The initial stereoinformation of the natural amino acids used as starting materials in the synthesis of **2**–**6** is lost most likely during activation by ethyl chloroformate. Racemization *via* the well-known azlacton mechanism and reaction with **1** lead to

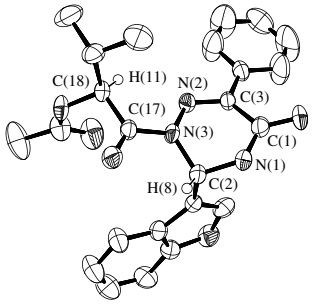


Figure 1 ORTEP diagram of the X-ray crystal structure of product **3**.[§]

[†] Acetylamino acids and starting triazinone **1** were synthesised by known procedures. TLC analysis was performed on Merck silica gel $60F_{254}$ plates and visualised by exposure to UV light. Column chromatography was conducted with Merck silica gel 60. ^{1}H and ^{13}C NMR spectra were recorded with Bruker WH-250, AC-300 and AC-600 instruments. Melting points were measured on a Boetius apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer model 341 polarimeter.

General procedure for the synthesis of **2**–**6**: to a magnetically stirred suspension of the *N*-acetylamino acid (1 mmol) in 3 ml of THF at room temperature NEt_3 (1.2 mmol) was added. The solution was cooled to 0 °C in an ice bath and $ClCO_2Et$ (1.1 mmol) was added. After 5 min, triazinone **1** (1 mmol) and indole (1.1 mmol) were added. After 30 min, the ice bath was removed and the reaction mixture was stirred for 12–18 h at room temperature (control by TLC). The precipitate formed was filtered off anf then, in case of **2**–**4**, washed with THF and water, recrystallised from DMF and dried. In case of **5** and **6**, the mother liquid was evaporated and the residue oil purified by column chromatography on silica gel with ethyl acetate as a solvent. Then the solution was evaporated, the residue oil crystallised from diethyl ether and the resulting solid was dried.

racemic acyltriazinones as reaction intermediates. The reaction proceeds equally in the absence of amino acids as acylation reagents; ethyl chloroformate and **1** yield an intermediate ethyl carbamate, which subsequently reacts with the nucleophile leading to **7** (Scheme 2).¶

We supposed the use of naproxen **8** as an acylation agent would allow to avoid racemization of the stereo centre in the starting material in the course of the reaction. The observed optical rotation ($[\alpha]_D^{20}$ –590, *c* 0.7) of reaction product **9** indicated that this assumption was valid (Scheme 3). The HPLC analysis of **9** showed a 98:2 ratio between *SS* and *SR*.††

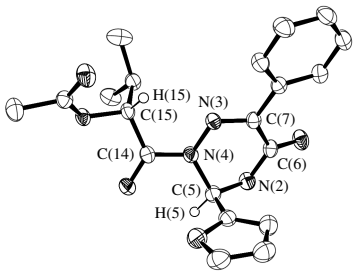


Figure 2 ORTEP diagram of the X-ray crystal structure of product **6**.§

‡ *2-(2-Acetamido-4-methylpentanoyl)-3-(1*H*-indol-3-yl)-6-phenyl-3,4-dihydro-2*H*-[1,2,4]triazin-5-one* **2**: yield, 49%; white solid; mp 256–257 °C; R_f 0.6 (ethyl acetate). ^{1}H NMR (600 MHz, [$^2H_6$]DMSO) δ: 0.89 (d, 3H, Me, *J* 6.6 Hz), 0.92 (d, 3H, Me, *J* 6.6 Hz), 1.47–1.52 (m, 1H, CH_2), 1.61–1.66 (m, 1H, CH_2), 1.72–1.79 (m, 1H, CH), 1.88 (s, 3H, COMe), 5.52–5.62 (m, 1H, CH), 6.96 (t, 1H, indole, *J* 7.3 Hz), 7.04 (t, 1H, indole, *J* 7.3 Hz), 7.13 (d, 1H, indole, *J* 2.1 Hz), 7.17 [d, 1H, C(3)H, *J* 5.4 Hz], 7.28 (d, 1H, indole, *J* 8.1 Hz), 7.29–7.36 (m, 3H, Ph), 7.72 (d, 1H, indole, *J* 8.1 Hz), 7.89–7.90 (m, 2H, Ph), 8.03 (d, 1H, NH, *J* 8.1 Hz), 9.74 [d, 1H, N(4)H, *J* 5.4 Hz], 10.87 (d, 1H, NH, indole, *J* 1.6 Hz). ^{13}C NMR (150 MHz, [$^2H_6$]DMSO) δ: 21.01, 22.22, 23.05, 24.44, 48.01, 59.01, 111.47, 111.70, 119.02, 119.05, 121.52, 124.00, 124.46, 127.64, 127.99, 129.36, 132.25, 136.66, 144.01, 155.41, 169.48, 172.46. Found (%): C, 67.14; H, 5.90; N, 15.87. Calc. for $C_{25}H_{27}N_5O_3$ (%): C, 67.40; H, 6.11; N, 15.72.

*2-(2-Acetamido-3-methylbutanoyl)-3-(1*H*-indol-3-yl)-6-phenyl-3,4-dihydro-2*H*-[1,2,4]triazin-5-one* **3**: yield, 76%; yellow solid; mp 276 °C; R_f 0.6 (ethyl acetate). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 0.97 (t, 6H, 2Me, *J* 6.4 Hz), 1.89 (s, 3H, COMe), 2.07–2.18 (m, 1H, CH), 5.41 (dd, 1H, CH, *J* 8.4 and 6.4 Hz), 6.95–7.05 (m, 1H, indole), 7.06–7.16 (m, 1H, indole), 7.22 [d, 1H, C(3)H, *J* 5.5 Hz], 7.24 (d, 1H, indole, *J* 2.6 Hz), 7.35 (d, 1H, indole, *J* 8.0 Hz), 7.41–7.53 (m, 3H, Ph), 7.71 (d, 1H, indole, *J* 8.0 Hz), 7.94–7.80 (m, 2H, Ph), 8.23 (d, 1H, NH, *J* 8.4 Hz), 9.86 [d, 1H, N(4)H, *J* 5.5 Hz], 11.19 (d, 1H, NH, indole, *J* 2.2 Hz). ^{13}C NMR (150 MHz, [$^2H_6$]DMSO) δ: 17.79, 19.27, 22.14, 30.44, 45.59, 53.87, 58.69, 111.54, 111.72, 118.97, 121.53, 124.22, 124.33, 127.80, 128.01, 129.44, 132.20, 136.60, 144.05, 155.21, 169.51, 171.31. Found (%): C, 66.99; H, 5.88; N, 16.13. Calc. for $C_{24}H_{25}N_5O_3$ (%): C, 66.81; H, 5.84; N, 16.23.

*2-(2-Acetamido-3-methylbutanoyl)-3-(1-methylindol-3-yl)-6-phenyl-3,4-dihydro-2*H*-[1,2,4]triazin-5-one* **4**: yield, 40%; yellow solid; mp 246–247 °C; R_f = 0.6 (ethyl acetate). ^{1}H NMR (300 MHz, [$^2H_6$]DMSO) δ: 1.00 (d, 6H, 2Me, *J* 6.8 Hz), 1.90 (s, 3H, COMe), 2.09–2.23 (m, 1H, CH), 3.72 (s, 3H, NMe), 5.41 (dd, 1H, CH, *J* 8.4 and 6.2 Hz), 6.99–7.04 (m, 1H), 7.10–7.17 (m, 3H), 7.27–7.30 (m, 1H), 7.37–7.39 (m, 3H, Ph), 7.75 (m, 1H), 7.92–7.99 (m, 3H), 9.69 (d, 1H, NH, *J* 5.6 Hz). Found (%): C, 67.61; H, 6.04; N, 15.88. Calc. for $C_{25}H_{27}N_5O_3$ (%): C, 67.40; H, 6.11; N, 15.72.

*2-[2-Acetamido-3-(1*H*-indol-3-yl)propanoyl]-3-(1*H*-indol-3-yl)-6-phenyl-3,4-dihydro-2*H*-[1,2,4]triazin-5-one* **5**: yield, 32%; white solid; mp 173–174 °C; R_f 0.4 (ethyl acetate). ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 1.87 (s, 3H, MeCO), 3.10–3.29 (m, 2H, CH_2), 5.71–5.80 (m, 1H, CH), 6.74–6.79 (m, 1H), 6.96–7.11 (m, 3H), 7.15–7.18 (m, 3H), 7.25–7.46 (m, 6H), 7.76–7.81 (m, 3H), 8.18 (d, 1H, NH, *J* 5.6 Hz), 9.62 (d, 1H, NH, *J* 5.3 Hz), 10.63 (br. s, 1H, NH), 10.98 (br. s, 1H, NH). Found (%): C, 69.55; H, 5.07; N, 16.33. Calc. for $C_{30}H_{26}N_6O_3$ (%): C, 69.48; H, 5.05; N, 16.21.

*2-(2-Amino-3-methylbutanoyl)-6-phenyl-3-(1*H*-pyrrol-2-yl)-3,4-dihydro-2*H*-[1,2,4]triazin-5-one* **6**: yield, 30%; white solid; mp 224–225 °C; R_f 0.6 (ethyl acetate). ^{1}H NMR (600 MHz, CD_3OD) δ: 1.05 (d, 3H, Me, *J* 6.88 Hz), 1.06 (d, 3H, Me, *J* 6.88 Hz), 2.06 (s, 3H, COMe), 2.26 (dqq, 1H, CH, *J* 5.67, 6.87 and 6.86 Hz), 5.45 (d, 1H, CH, *J* 5.69 Hz), 6.02 [dd, 1H, C(4′)H, pyrrole, *J* 3.51 and 2.73 Hz], 6.15 [ddd, 1H, C(3′)H, pyrrole, *J* 3.51, 1.58 and 0.94 Hz], 6.75 [ddd, 1H, C(5′)H, pyrrole, *J* 2.73, 1.58 and 0.48 Hz], 7.08 [dd, 1H, C(3)H, *J* 0.94 and 0.48 Hz], 7.39–7.45 (m, 3H, Ph), 7.88–7.90 (m, 2H, Ph). ^{13}C NMR (150 MHz, CD_3OD) δ: 18.16, 19.84, 22.29, 32.07, 56.82, 60.54, 108.72, 109.79, 120.82, 128.67, 129.17, 129.66, 131.09, 133.69, 146.06, 157.92, 173.69, 173.90. Found (%): C, 62.73; H, 6.06; N, 18.43. Calc. for $C_{20}H_{23}N_5O_3$ (%): C, 62.98; H, 6.08; N, 18.36.

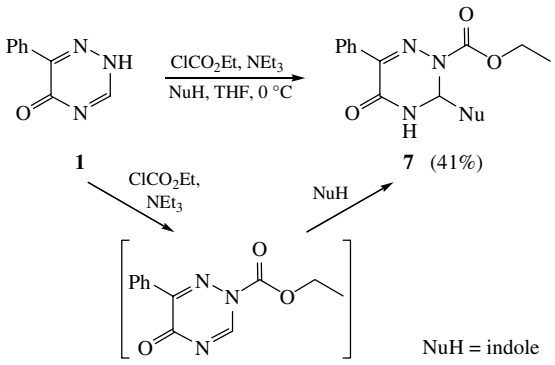
§ *X-ray diffraction data for* **3**. $C_{24}H_{24}N_5O_3$, *M* = 430.48, triclinic, space group *P*1, *a* = 8.881(2), *b* = 11.0359(18) and *c* = 11.5092(16) Å, *V* = = 1080.2(4) Å^3, *Z* = 2, d_{calc} = 1.324 g cm^{-3}, μ = 0.832 mm^{-1}, *F*(000) = 454. Data collection was performed at 295 K within the θ range from 2.62 to 31.77°; a total of 14931 reflections (of which 2063 were unique) were collected [*R*(int) = 0.0547] and used to refine 337 parameters. The structure was solved with the SHELXS-97 program and refined using SHELXL-97.

X-ray diffraction data for **6**. $C_{20}H_{22}N_5O_3$, *M* = 380.43, monoclinic, space group $P2_1/a$, *a* = 9.62160(10), *b* = 19.08220(10) and *c* = 10.78380(10) Å, *V* = 1974.54(3) Å^3, *Z* = 4, d_{calc} = 1.280 g cm^{-3}, μ = 0.727 mm^{-1}, *F*(000) = 804. Data collection was performed at 123 K within the θ range from 2.3119 to 62.1351°; a total of 28335 reflections (of which 3103 were unique) were collected [*R*(int) = 0.0253] and used to refine 256 parameters. The structure was solved with the SIR-97 program and refined using SHELXL-97.

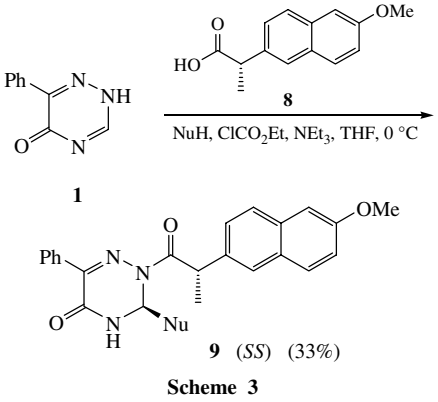
CCDC 672106 and 649200 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

¶ *Procedure for the synthesis of ethyl 3-(1*H*-indol-3-yl)-5-oxo-6-phenyl-4,5-dihydro-3*H*-[1,2,4]triazine-2-carboxylate* **7**. To a magnetically stirred suspension of triazinone **1** (1 mmol) in 3 ml THF cooled to 0 °C, $ClCO_2Et$ (1.1 mmol) and NEt_3 (1.2 mmol) were added. Then indole (1.1 mmol) was added. After 30 min the ice bath was removed and the reaction mixture was stirred at room temperature for 12–18 h (monitoring by TLC). The formed precipitate was filtered off, washed with THF. The resulting solution was evaporated, the residue oil purified by column chromatography on silica gel with $CHCl_3$ (R_f 0.1) and ethyl acetate (R_f 0.7) as eluents and recrystallised from diethyl ether. Yield, 41%; white solid; mp 168–169 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.05 (t, 3H, Me, *J* 7.1 Hz), 4.05 (dq, 2H, CH_2, *J* 7.1 and 1.0 Hz), 6.68–6.84 (m, 4H), 6.98–7.04 (m, 4H), 7.47 (d, 1H, *J* 7.9 Hz), 7.53–7.69 (m, 2H, Ph), 9.07 [d, 1H, N(4)H, *J* 5.4 Hz], 10.25 (s, 1H, NH, indole). Found (%): C, 66.31; H, 4.98; N, 15.55. Calc. for $C_{20}H_{18}N_4O_3$ (%): C, 66.29; H, 5.01; N, 15.46.

†† *Procedure for the synthesis of 3-(1*H*-indol-3-yl)-2-[2-(6-methoxynaphthalen-2-yl)propionyl]-6-phenyl-3,4-dihydro-2*H*-[1,2,4]triazin-5-one* **9**. To a magnetically stirred solution of naproxen (1 mmol) in 3 ml THF at room temperature NEt_3 (1.2 mmol) was added. The solution was cooled to 0 °C and $ClCO_2Et$ (1.1 mmol) was added. After 5 min, triazinone **1** (1 mmol) and indole (1.1 mmol) were added. After 30 min, the ice bath was removed and the reaction mixture was stirred for 12–18 h at room temperature (monitoring by TLC). The precipitate formed was filtered off, washed with THF. The mother liquid was evaporated, dissolved in $CHCl_3$ and purified using a silica gel column with $CHCl_3$ (R_f 0.1) and ethyl acetate (R_f 0.8) as eluents. Yield, 33%; white solid; mp 235–236 °C; $[\alpha]_D^{20}$ –590 (*c* 0.7, MeCN); diastereomeric ratio of 98:2 (HPLC: Lichrosorb S, hexane/isopropil alcohol, 16:1, 1.0 cm^3 min^{-1}, λ = 254 nm). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55 (d, 3H, CMe, *J* 7.0 Hz), 3.82 (s, 3H, OMe), 4.82 (q, 1H, CH, *J* 6.9 Hz), 6.73–6.74 (m, 1H), 6.87–7.06 (m, 4H), 7.22–7.34 (m, 7H), 7.44 (s, 1H), 7.51–7.54 (m, 1H), 7.67–7.70 (m, 1H), 7.80–7.84 (m, 2H, Ph), 9.52 (d, 1H, NH, *J* 5.2 Hz), 10.81 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 18.92, 41.31, 54.68, 58.09, 104.88, 111.20, 112.37, 118.13, 118.93, 119.24, 121.59, 123.68, 124.03, 125.23, 126.24, 126.39, 127.48, 128.03, 128.09, 128.45, 129.11, 132.37, 132.66, 135.66, 136.35, 143.37, 155.41, 156.80, 172.65. Found (%): C, 74.15; H, 5.16; N, 11.33. Calc. for $C_{31}H_{26}N_4O_3$ (%): C, 74.09; H, 5.21; N, 11.15.



Scheme 2



Scheme 3

In summary, we have extended the use of triazinones as starting materials in heterocylic synthesis. Activation of the triazinone by natural amino acids or naproxen and subsequent addition of a nucleophile lead to 2-acyl-3-indolyl-6-phenyl-3,4-dihydro-1,2,4-triazin-5(4*H*)-ones in diastereomerically pure form. The relative stereochemistry was determined by an X-ray analysis.

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