Synthesis of 2-Amino-Imidazo[1,2-*b*] [1,2,4]Triazine-3,6,7(5*H*)-Triones

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ABSTRACT

3,6-Diaminosubstituted 1,2,4-triazin-5-ones **2** react with ethyl oxalyl chloride in the presence of imidazole as a base to form imidazo[1,2-*b*][1,2,4]triazine-3,6,7(5*H*)-triones **5.**

INTRODUCTION

Fused 1,2,4-triazines have gained considerable interest in medicinal chemistry and agrochemistry because of their various biological effects. For instance, pyrrolo[2,1-*f*][1,2,4]triazines (1-7), pyrrolo[2,1-*c*][1,2,4]triazines (8, 9), and pyrrolo[1,2-f][1,2,4]triazines (10) have been found to display strong antitumor activity, whilst pyrazolo[5,1-*c*][1,2,4]triazines exhibit antifungal (11) as well as antiproliferative activity (12). In recent years, imidazo-condensed 1,2,4-triazines have been characterized as $GABA_A$ receptor ligands (13), as polo-like kinase inhibitor (14) and as inhibitors of AMP deaminase (15), the latter being promising compounds for the development of novel anticancer agents.

During our research directed to novel bioactive agents derived from functionalized 1,2,4-triazines we became interested in imidazo[1,2-*b*][1,2,4]triazine derivatives **5,** and report herein a facile synthetic route to the title compounds.

As shown recently (16), the ultrasound-promoted cyclocondensation of N^1-amino-N^2-arylmethyl-guanidin-hydroiodides **1** with ethyl 2-amino-2-thioxoacetate delivers 3,6-diami-nosubstituted 1,2,4-triazin-5-ones **2,** which were found to undergo regioselective acylation at N-2 affording compounds of type **3** (Scheme 1).

Taken into account these results, we investigated the corresponding acylation of **2** with ethyl oxalyl chloride, expecting the formation of imidazo-condensed 1,2,4-triazines **5** via cyclocondensation of an assumed intermediate **4.**

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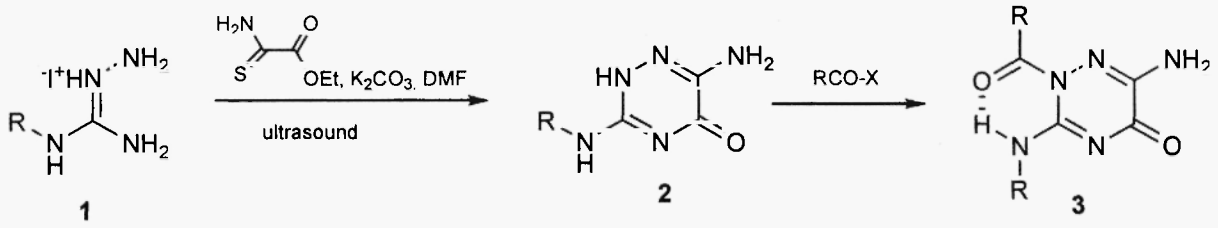
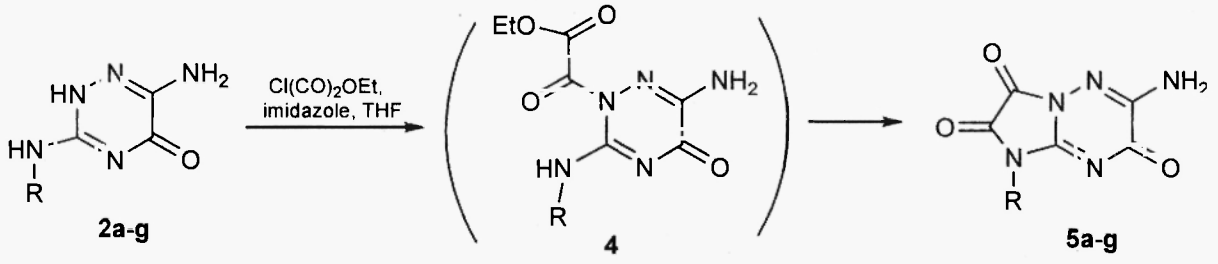


Scheme 1. Synthesis and acylation of 3,6-diaminosubstituted 1,2,4-triazin-5-ones **2**

When the 1,2,4-triazinones **2a-g** were dissolved with ethyl oxalyl chloride in anhydrous tetrahydrofuran in the presence of imidazole as a base, the reaction mixture became intensively yellow-coloured, displaying a sharp (C=O)-absorption band at 1800 cm^{-1} in the IR-spectrum, which indicated the formation of the desired imidazo[1,2-*b*][1,2,4]triazine-3,6,7(5*H*)-triones **5a-g**. After filtration, evaporation of the solvent and recrystallization of the remaining solids, the aimed novel heterocycles **5a-g** were obtained as shiny-yellow crystals in 40-64 % yield. Unambiguous structural assignment of **5a-g** is based on microanalytical data, IR, ^{1}H NMR, ^{13}C NMR and MS spectra. In addition, structure of **5d** has been proven by X-ray analysis (**Figure 1**).



Scheme 2. Synthesis of imidazo[1,2-*b*][1,2,4]triazine-3,6,7(5*H*)-triones **5a-g**

Table 1
5-Substituted 2-amino-imidazo[1,2-*b*][1,2,4]triazin-3,6,7(5*H*)-triones **5a-g**

Compound	R	Yield (%)
5a	4-F-Bn	61
5b	4-F-Phenethyl	48
5c	4-Cl-Bn	52
5d	Bn	64
5e	4-Methyl-Bn	64
5f	Thiophen-2-ylmethyl	40
5g	1-Naphthyl	52

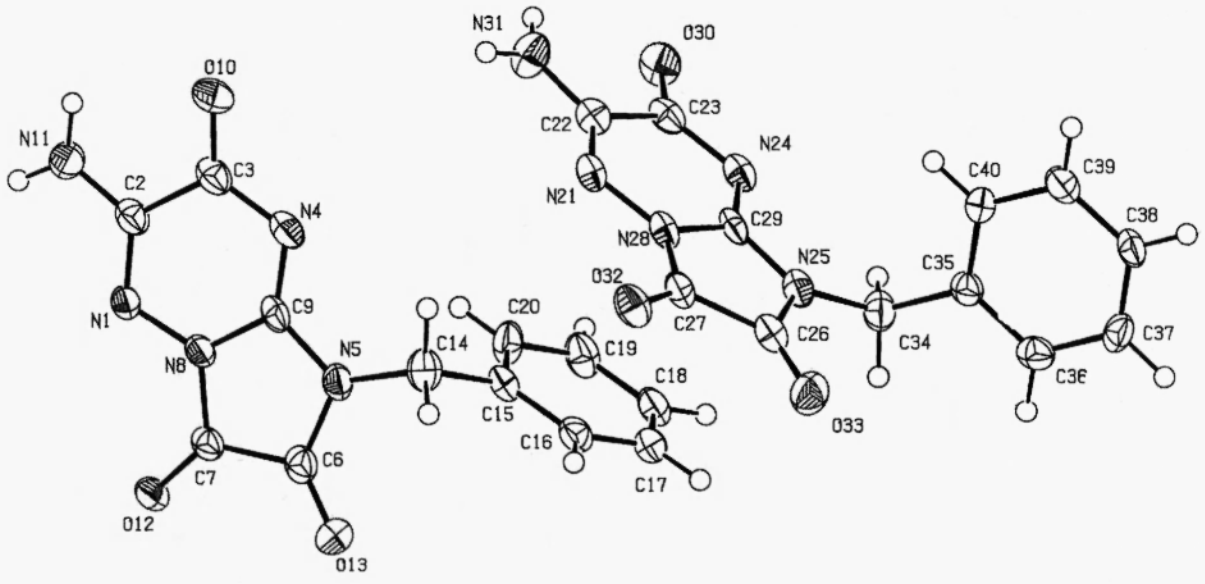


Fig. 1: X-ray Crystal structure of compound **5d**

EXPERIMENTAL

Melting points (uncorrected) were determined on a Mettler FP 62 apparatus. Elemental analyses were carried out with an EA 1108 CHNS-O instrument. IR spectra were recorded on a Varian 800 FT-IR. ^{1}H NMR (400 MHz) and ^{13}C NMR (100MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as internal standard and DMSO-d_6 as solvent. X-ray structure was determined with a Bruker SMART APEX CCD, rays Mo-Kα, wavelength 0.71073 Å, temperature 100 K (Oxford Cryosystem, 700 series Cryostream Cooler). CCDC 763442 contains the crystallographic data of compound **5d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure for preparation of compound 5:

1.5 mmol of imidazole were dissolved in 3 mL anhydrous THF, 1 mmol of compound **2** was added and the suspension stirred for two minutes. 1.5 mmol of ethyl oxalyl chloride in 2 mL anhydrous THF were added dropwise and the reaction mixture was stirred for 24 hours. The reaction batch was filtered and the filtrate concentrated in vacuum. The product crystallized from dichloromethane/tetrahydrofuran and was recrystallized from acetonitrile/diethyl ether.

2-Amino-5-(4-fluorobenzyl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5a**): Yield: 61 %, shiny yellow solid – mp. 227 °C - IR (KBr): ν = 3377, 3300 (NH), 1797, 1702, 1629 cm^{-1} (C=O) - ^{1}H NMR δ(ppm): 4.79 (s, 2H, CH_2N), 7.16-7.48 (m, 6H, Ar-H and NH_2). - ^{13}C NMR δ(ppm): 41.74 (CH_2N), 115.53 (d, $^{2}J_{C\text{-}F}$ = 21.36 Hz, CH arom), 130.24 (d, $^{3}J_{C\text{-}F}$ = 8.39 Hz, CH arom), 131.44 (d, $^{4}J_{C\text{-}F}$ = 3.05 Hz, Cquat), 148.89 (Cquat, C-2), 150.38 (Cquat, C-6), 155.22 (Cquat, C-7), 156.48 (Cquat, C-3), 159.06 (Cquat), 161.14 (d, $^{1}J_{C\text{-}F}$ = 242.63 Hz, CF). - $C_{12}H_8FN_5O_3$ (289.23): calcd. [%] C 49.83; H 2.79; N 24.21. found [%] C 49.74; H 2.90; N 24.10.

2-Amino-5-(4-fluorophenethyl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5b**): Yield: 48 %, shiny yellow solid – mp. 262 °C - IR (KBr): ν = 3475, 3327 (NH), 1795, 1701 cm^{-1} (C=O) - ^{1}H NMR δ(ppm): 2.91 (t, 3H, J = 7.5 Hz,

NCH_2CH_2), 3.79 (t, 3H, J = 7.5 Hz, NCH_2CH_2), 7.10-7.36 (m, 6H, Ar-H and NH_2). - ^{13}C NMR δ(ppm): 32.19 (NCH_2CH_2), 40.08 (NCH_2CH_2), 115.15 (d, $^2J_{C-F}$ = 21.22 Hz, CH arom), 130.62 (d, $^3J_{C-F}$ = 8.05 Hz, CH arom), 133.92 (d, $^4J_{C-F}$ = 2.93 Hz, Cquat), 148.48 (Cquat, C-5), 149.88 (Cquat, C-2), 154.47 (Cquat, C-6), 156.05 (Cquat, C-7), 158.64 (Cquat, C-3) (Cquat), 161.07 (d, $^1J_{C-F}$ = 242.24 Hz, CF). –$C_{13}H_{10}FN_5O_3$ (303.25): calcd. [%] C 51.49; H 3.32; N 23.09. found [%] C 51.46; H 3.61; N 22.93.

2-Amino-5-(4-chlorbenzyl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5c**): Yield: 52 %, shiny yellow solid – mp. 235 °C - IR (KBr): ν = 3485, 3370 (NH), 1794 cm^{-1} (C=O) - ^1H NMR δ(ppm): 4.80 (s, 2H, CH_2N), 7.17 (s, 2H, NH_2), 7.41-7.48 (m, 4H, Ar-H). - ^{13}C NMR δ(ppm): 41.29 (CH_2N), 128.22, 129.46 (CH arom), 132.20, 133.79, 148.44 (Cquat, C-5), 149.90 (Cquat, C-2), 154.75 (Cquat, C-6), 155.97 (Cquat, C-7), 158.57 (Cquat, C-3). –$C_{12}H_8ClN_5O_3$ (305.68): calcd. [%] C 47.15; H 2.64; N 22.91. found [%] C 47.01; H 2.79; N 22.78.

2-Amino-5-(benzyl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5d**): Yield: 64 %, shiny yellow solid – mp. 234 °C - IR (KBr): ν = 3481, 3300 (NH), 1803 cm^{-1} (C=O) - ^1H NMR δ(ppm): 4.80 (s, 2H, CH_2N), 7.16 (s, 2H, NH_2), 7.28-7.45 (m, 5H, Ar-H). - ^{13}C NMR δ(ppm): 42.45 (CH_2N), 128.00, 128.75 (CH arom), 135.22, 148.89 (Cquat, C-5), 150.39 (Cquat, C-2), 155.28 (Cquat, C-6), 156.57 (Cquat, C-7), 159.10 (Cquat, (C-3)). – $C_{12}H_9N_5O_3$ (271.24): calcd. [%] C 53.14; H 3.34; N 25.82. found [%] C 53.25; H 3.66; N 25.71.

2-Amino-5-(4-methylbenzyl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5e**): Yield: 64 %, shiny yellow solid – mp. from 240 °C decomposition - IR (KBr): ν = 3437, 3312 (NH), 1786 cm^{-1} (C=O) - ^1H NMR δ(ppm): 2.28 (s, 3H, Ar-CH_3), 4.74 (s, 2H, CH_2N), 7.15-7.31 (m, 6H, Ar-H and NH_2). - ^{13}C NMR δ(ppm): 20.58 (Ar-CH_3), 41.78 (CH_2N), 127.57, 128.80 (CH arom), 131.73, 136.74, 148.40 (Cquat, C-5), 149.91 (Cquat, C-2), 154.77 (Cquat, C-6), 156.09 (Cquat, C-7), 158.63 (Cquat, C-3)). – $C_{13}H_{11}N_5O_3$ (285.26): calcd. [%] C 54.74; H 3.89; N 24.55. found [%] C 54.69; H 4.01; N 24.38.

2-Amino-5-(thiophen-2-ylmethyl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5f**): Yield: 40 %, shiny red solid – mp. 221 °C - IR (KBr): ν = 3423, 3371 (NH), 1794 cm^{-1} (C=O) - ^1H NMR δ(ppm): 4.96 (s, 2H, CH_2N), 6.99-7.49 (m, 5H, Ar-H and NH_2). - ^{13}C NMR δ(ppm): 36.77 (CH_2N), 126.58, 126.70, 127.95 (CH arom), 136.13, 148.40 (Cquat, C-5), 149.74 (Cquat, C-2), 154.26 (Cquat, C-6), 155.63 (Cquat, C-7), 158.54 (Cquat, C-3)). –$C_{10}H_7N_5O_3S$ (277.26): calcd. [%] C 43.32; H 2.54; N 25.26; S 11.56. found [%] C 43.12; H 2.69; N 25.20; S 11.52.

2-Amino-5-(naphthalen-1-yl)imidazo[1,2-b][1,2,4]triazine-3,6,7(5H)-trione (**5g**): Yield: 52 %, shiny yellow solid – mp. > 300 °C - IR (KBr): ν = 3462, 3327 (NH), 1793 cm^{-1} (C=O) - ^1H NMR δ(ppm): 7.25 (s, 2H, NH_2), 7.58-8.27 (m, 7H, Ar-H). - ^{13}C NMR δ(ppm): 123.36, 125.59 (CH arom), 126.51 (Cquat), 126.86, 127.10, 127.19, 128.09 (CH arom), 130.14 (Cquat), 133.75 (CH arom), 148.76 (Cquat, C-5), 150.16 (Cquat, C-2), 154.64 (Cquat, C-6), 156.37 (Cquat, C-7), 158.73 (Cquat, C-3)). – $C_{15}H_9N_5O_3$ (307.07): calcd. [%] C 58.63; H 2.95; N 22.79. found [%] C 58.68; H 3.01; N 22.93.

CONCLUSION

In analogy to the recent finding (16) that 3,6-diaminosubstituted 1,2,4-triazin-5-ones **2** are acylated regioselectively at N-2, the corresponding reaction of **2** with ethyl oxalyl chloride also occured primarily at N-2 to form an intermediate **4**, which upon subsequent cyclization gave rise to the formation of novel imidazo[1,2-*b*][1,2,4]triazine-3,6,7(5*H*)-triones **5** in reasonable yields.

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