Novel 6-azapteridines and oxazinotriazines from bifunctional 1,2,4-triazines

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Dedicated in friendship to Prof. Zhi-Tang Huang on the occasion of his 75th birthday
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Abstract
Ethyl 5-amino-1,2,4-triazine-6-carboxylates **1a-b** undergo condensation with aryl isocyanates **2a-b** to afford the corresponding pyrimido[4,5-*e*][1,2,4]triazines **3a,b**. Alternatively, **1a-b** reacted with triphenylphosphine and hexachloroethane to afford the corresponding iminophosphoranes **6a-b**, of which **6a** with excess benzoyl chloride **7** afforded the 3,1-oxazino[6,5-*e*][1,2,4]triazine **8a**.

Keywords: Fused heterocycles, 1,2,4-triazine, pyrimido[4,5-*e*][1,2,4]triazine, 6-azapteridine, 3,1-oxazino[6,5-*e*][1,2,4]triazine, ethyl 5-amino-1,2,4-triazin-6-carboxylate, ethyl 5-(triphenylphosphoranylideneamino)-1,2,4-triazine-6-carboxylate

Introduction

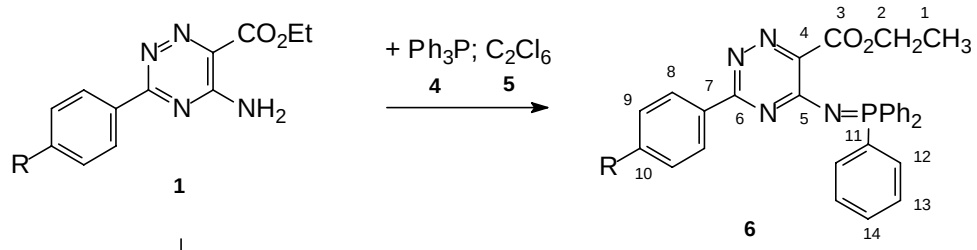
Many 1,2,4-triazine derivatives are well known to possess biological activities. Thus, several 5-amino-1,2,4-triazine-5-ones have found use as herbicides with high selectivity.[1,2] In the last decade as-triazines have been screened *in vitro* supporting their anti-HIV and anti-cancer activities.[3-6] Furthermore, pyrimido-triazines possess significant biological activities, such as the antibiotica fervenuline, reumycine, toxoflavine, and methylfervenuline showing all a pyrimido[5,4-*e*][1,2,4]triazine (7-azapteridine) ring system, while several Pyrimido[4,5-*e*][1,2,4]triazines (6-azapteridines) exhibit antibacterial activity.[7-9] From these both isomers, the 6-azapteridines so far have been less studied. The synthetic approach to 6-azapteridines can be realized in three general routes: (1) starting from a pyrimidine-, (2) from a triazine-precursor, or (3) from a purine moiety.[10, 11]

In the present study we have performed a pyrimido-annelation to an existing 1,2,4-triazine derivative by [4+2]-condensation reaction of ethyl 5-amino-1,2,4-triazine-6-carboxylates **1a-b**

with aromatic isocyanates **2a-b**. Another two-step conversion of **1a** via iminophosphorane **6a** resulted in the formation of a 3,1-oxazino[6,5-*e*][1,2,4]triazine **8a**.

Results and Discussion

Recently, we have reported the synthesis of ethyl 5-amino-1,2,4-triazine-6-carboxylate **1**.[12]. As all heterocyclic β-enamino esters, **1a-b** have two reactive centers which enables them to different cyclization reactions, [1, 3] as e.g. upon refluxing with isocyanates [13, 14] **2** in pyridine leading in high yield (> 80%) to the pyrimido[4,5-*e*][1,2,4]triazines **3a-b.**



1, 3, 6, 8	R	R'
a	Cl	H
b	CH_3O	Cl

Scheme 1

With the aid of triphenylphosphine/hexachloroethane **1a-b** are smoothly converted into the versatile 3-(triphenylphosphoranylideneamino)-derivatives **6a-b** [13, 16] (cf. Scheme 1). Aza-Wittig-reaction of **6a** in excess benzoyl chloride **7** as solvent and reactand with traces of DMAP leads in good yield (60%) to the oxazino-triazine ring system **8a** (cf. Scheme 1).

Experimental Section

3-(4'-Chlorophenyl)-7-phenylpyrimido[4,5-*e*][1,2,4]triazine-(5H,7H)-6,8-dione (3a). 0.28 g (1 mmol) of **1a** is reacted in 20 ml pyridine with 0.22 ml (240 mg, 2 mmol) phenylisocyanate **2a** and refluxed for 10 h. Upon cooling down a yellow-green solid precipitates which is recrystallized from ethanol; yield: 0.31 g, (88%), mp 377-380°C.- yellow crystals; MS (m/z, %): 351.0 (M^+, 48%), 119.0 ($C_7H_5NO^+$, 100%); IR (KBr), [cm^{-1}]: 3427.6, 1741.3, 1690.9; UV (EtOH): λ_{max} [nm] (lg ε): 333.0 (4,14); ^{1}H NMR (400 MHz, d_6-DMSO): δ = 7.40-7.45 (m, 3H, 13-,14-,15-H), 7.51-7.45 (m, 2H, 12-, 16-H), 7.79 (d, 2H, 8 Hz, 8-H), 8.54 (d, 2H, 8 Hz, 9-H), 13.09 (s, 1H, 3-H); ^{13}C NMR (100 MHz, d_6-DMSO): δ = 123.8 (C-13), 128.6 (C-15), 129.1 (C-12), 129.4 (C-16), 130.2 (C-14), 132.6 (C-8), 134.8 (C-9), 136.1 (C-7), 136.7 (C-11), 137.7 (C-10), 149.5 (C-4), 149.8 (C-6), 150.7 (C-5), 159.1 (C-2), 162.3 (C-1). Anal. calcd for $C_{17}H_{10}ClN_5O_2$: C, 58.05; H, 2.87; N, 19.91. Found: C, 58.27; H, 2.94; N, 19.82.

7-(4'-Chlorphenyl)-3-(4'-methoxyphenyl)pyrimido[4,5-*e*][1,2,4]triazine-(5H,7H)-6,8-dione (3b). 0.29 g (1 mmol) **1b** is refluxed for 8 h in 20 ml pyridine with 0.33 g (2 mmol) 4-chlorphenyl-isocyanate **2b** . Upon cooling down to ambient temp. a yellow precipitate is obtained which is recrystallized from ethanol; yield: 0.33 g, (81%), mp 339-340°C.- yellow crystals; MS (m/z, %): 381.0 (M^+, 38%), 153.1 ($C_7H_4ClNO^+$, 100%); IR (KBr), [cm^{-1}]: 3400.6, 1748.5, 1692.5; UV (EtOH): λ_{max} [nm] (lg ε): 354.0 (4,35); ^{1}H NMR (300 MHz, d_6-DMSO): δ = 3.87 (s, 3H, CH_3O), 7.19 (d, 2H, 8.7 Hz, 12-H), 7.39 (d, 2H, 8.5 Hz, 9-H), 7.60 (d, 2H, 8.5 Hz, 8-H), 8.47 (d, 2H, 8.7 Hz, 13-H), 12.81 (s, 1H, 3-H); ^{13}C NMR (75 MHz, d_6-DMSO): δ = 56.0 (CH_3O), 115.2 (C-9), 126.4 (C-10), 129.6 (C-8), 131.0 (C-13), 131.1 (C-12), 133.7 (C-7), 134.3 (C-11), 136.1 (C-14), 136.2 (C-6), 150.2 (C-4), 151.0 (C-5), 159.6 (C-2), 163.5 (C-1). Anal. calcd for $C_{18}H_{12}ClN_5O_3$: C, 56.63; H, 3.17; N, 18.34. Found: C, 55.91; H, 2.83; N, 18.19.

Ethyl 3-(4'-chlorophenyl)-5-(triphenylphosphoranylideneamino)1,2,4-triazin-6-carboxylate (6a). 1.53 g (5.5 mmol) of **1a** is suspended in an Argon atmosphere in 120 ml absol. MeCN . Then are added in sequence 1.73 g (6.6 mmol) triphenylphosphane **4**, 1.6 ml (1.16 g, 11 mmol) triethylamine, and 1.3 g (5.5 mmol) hexachloroethane. After stirring for 16 h at room temp., the solution is refluxed for additional 5 h. Upon cooling down the precipitating triethylamine hydrochloride is removed by filtration. The resulting solution is evaporated to its half of volume and the yellow solid precipitating is filtered off, and recrystallized two times from ethanol; yield: 2.5 g, (84%), mp 192-193°C.- white crystals; MS (m/z, %): 538.2 (M^+, 11%), 262.2 ($C_{18}H_{15}P^+$, 100%); IR (KBr), [cm^{-1}]: 1731.0, 1475.5; UV ($CHCl_3$): λ_{max} [nm] (lg ε): 288.0 (4,52); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, 3H, 8 Hz, 1-H), 4,45 (q, 2H, 8 Hz, 2-H), 7.10-7.22 (m, 2H, 8-H), 7.31-7.58 (m, 10H), 7.65-7.80 (m, 7H, 9H, superimposed); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (C-1), 61.6 (C-2), 127.4 ($^3J_{PC}$= 13 Hz, C-13), 128.8 ($^1J_{PC}$= 101 Hz, C-11), 129.5 ($^4J_{PC}$= 6 Hz, C-14), 133.2 ($^2J_{PC}$= 10 Hz, C-12), 137.2 (C-10), 147.4 ($^2J_{PC}$= 22 Hz, C-5), 158.5 ($^4J_{PC}$= 7 Hz, C-6), 161,2 (C-4), 165.7 (C-3). Anal. calcd for $C_{30}H_{24}ClN_4O_2P$: C, 66.86; H, 4.49; N, 10.40. Found: C, 66.38; H, 4.01; N, 10.11.

Ethyl 3-(4'-methoxyphenyl)-5-(triphenylphosphoranylideneamino)1,2,4-triazine-6-carboxylate (6b). 1.65 g (6 mmol) of **1b** is suspended under Argon in 120 ml absol. MeCN. Then 1.89 g

(7.2 mmol) triphenylphosphine **4**, 1.7 ml (1.23 g, 12 mmol) triethylamine, and 1.42 g (6 mmol) hexachlorethane **5** are added. Working up similar to **6a**, gives 2.1 g, (65%), mp 152-153°C – light yellow crystals; MS (m/z, %): 534.2 (M^+, 29%), 262.1 ($C_{18}H_{15}P^+$, 100%); IR (KBr), [cm^{-1}]: 1729.6, 1466.9; UV ($CHCl_3$): λ_{max} [nm] (lg ε): 286.0 (4.47); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, 3H, 7 Hz, 1-H), 3.73 (s, 3H, CH_3O), 4.42 (q, 2H, 7 Hz, 2-H), 6.69 (d, 2H, 9 Hz, 9-H), 7.37-7.41 (m, 6H, 12-H), 7.47-7.51 (m, 3H, 14-H), 7.69 (d, 2H, 9 Hz, 8-H), 7.72-7.76 (m, 6H, 13-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (C-1), 55.3 (CH_3O), 61.4 (C-2), 113.5 (C-10), 114.1 (C-9), 128.7 ($^3J_{PC}$= 12 Hz, C-13), 130.0 ($^1J_{PC}$= 93 Hz ,C-11), 132.5 ($^4J_{PC}$= 3 Hz, C-14), 133.0 ($^2J_{PC}$= 10 Hz, C-12), 145.9 ($^2J_{PC}$= 22 Hz, C-5), 158.2 ($^4J_{PC}$= 6 Hz, C-6), 161.6 ($^3J_{PC}$= 23 Hz, C-4), 165.6 (C-3). Anal. calcd for $C_{31}H_{27}N_4O_3P$: C, 69.65; H, 5.09; N, 10.48. Found: C, 68.86; H, 5.27; N, 10.79.

3-(4'-Chlorphenyl)-6-phenyl-3,1-oxazino[6,5-*e*][1,2,4]triazine-(7H)8-one (8a)[a]. 0,54 g (1 mmol) iminophosphorane **6a** is heated for 4 h at 120°C in 4 ml (34 mmol) benzoyl chloride **7** after adding catalytic amounts of DMAP. After cooling down the product is filtered off, washed two times with diethylether, and recrystallized two times from absol. MeCN; yield 0.2 g (60%), mp 243-245°C.- yellow-green crystals; MS (m/z, %): 336.0 (M^+, 14%), 105.1 ($C_7H_5O^+$, 100%); IR (KBr), [cm^{-1}]: 1777.9, 1718.6; UV (CH_2Cl_2): λ_{max} [nm] (lg ε): 290.0 (4.46); ^{1}H NMR (300 MHz, d_6-DMSO): δ = 7.69 (t, 2H, 7 Hz, 12-H), 7.75 (d, 2H, 9 Hz 7-H), 7.83 (t, 1H, 7 Hz, 13-H), 8.35 (d, 2H, 7 Hz, 11-H), 8.61 (d, 2H, 9 Hz, 8-H). Anal. calcd for $C_{17}H_9ClN_4O_2$: C, 60.64; H, 2.69; N, 16.64. Found: C, 59.71; H, 2.63; N, 16.63.

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References and Notes

[a] due to low solubility of **8a**, no ^{13}C NMR measurements could be made.

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