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Synthesis of 3-amino-5*H*-pyrrolo[2,3-*e*]-1,2,4-triazines by Sonogashira/copper(I)-catalyzed heteroannulation

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Abstract—A Sonogashira/copper(I)-catalyzed heteroannulation sequence was developed to convert 3,5-diamino-6-chloro-1,2,4-triazines to the corresponding 3-amino-5*H*-pyrrolo[2,3-*e*]-1,2,4-triazine derivatives in good yields.

3-Aminopyrrolo[2,3-*d*]pyrimidine ring **1** is present in many anticancer agents recently described (dihydrofolate reductase or thymidylate synthase inhibitors, aurora kinase inhibitors, EGFR receptor inhibitors, HSP-90 inhibitors).[1] The pyrrolo[2,3-*e*]-1,2,4-triazine moiety can be considered as a bioisostere of this nucleus and is mainly encountered in 5*H*-1,2,4-triazino[5,6-*b*]-indole derivatives which also displayed pharmacological and biological properties.[2] These latter compounds have been widely prepared by condensation of isatine on thiocarbazide. As part of our ongoing programme directed towards the design of new kinase inhibitors, we have developed the synthesis of 6-substituted 3-amino-5*H*-pyrrolo[2,3-*e*]-1,2,4-triazines **2** as potential scaffolds for new anticancer agents (Fig. 1).

Few synthetic pathways of pyrrolo[2,3-*e*]-1,2,4-triazine or related nuclei have been reported in the literature.[3]

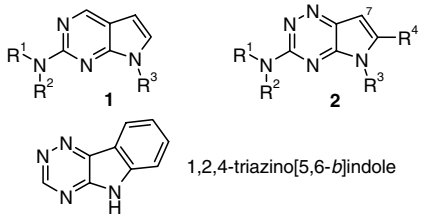

Figure 1.

Keywords: 1,2,4-Triazine; Alkyne; Palladium; Heteroannulation.
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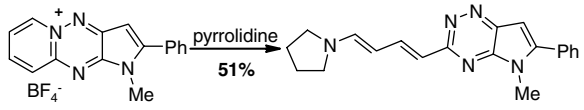
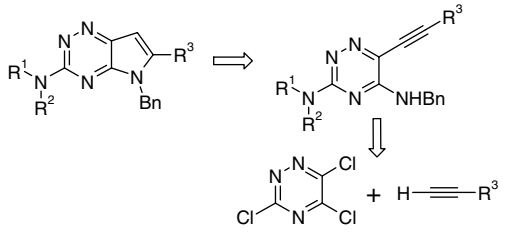


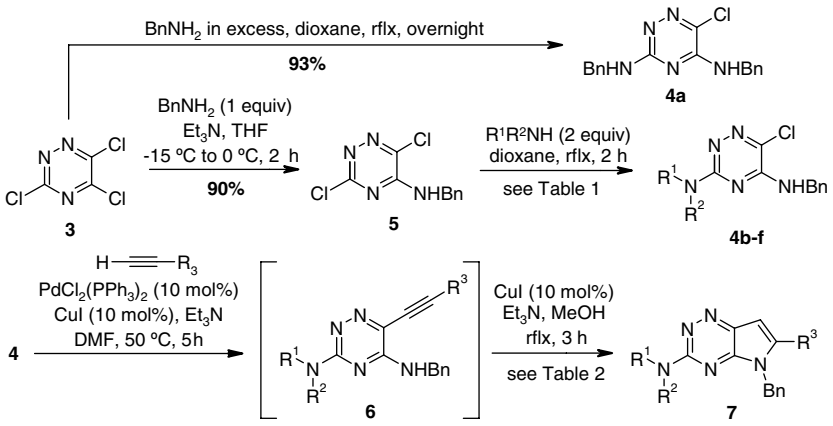
Scheme 1.

In 2003, the synthesis of 6-phenylpyrrolo[2,3-*e*]-1,2,4-triazine was described through a fragmentation reaction of 1-methyl-2-phenylpyrrolo[2,3-*e*]pyrido[1,2-*b*]-1,2,4-triazinium tetrafluoroborate (Scheme 1).[3c]

The undeniable success of the synthesis of indoles,[4] azaindoles[4b–d,5] and other related heterocycles[4b–d,6] by cyclization of appropriately functionalized *o*-aminoacetylenes, prepared by Sonogashira reaction of the corresponding aryl halide and terminal alkyne, prompted us to develop access to 6-substituted 3-amino-5*H*-pyrrolo[2,3-*e*]-1,2,4-triazine by the same way (Scheme 2). Final cyclization of the alkyne intermediate to reach the desired heterocycles should be effective either by iodocyclization[4e] or by base-mediated[4b–d,5c] or, by transition metal-mediated cyclization.[5a]



Scheme 2.



Scheme 3.

3,5-Diamino-6-chloro-1,2,4-triazines **4** were first obtained from the readily available 3,5,6-trichloro-1,2,4-triazine **3** (Scheme 3). This key precursor was prepared in two steps from the commercially available 6-azauracil.[7] Treatment of **3** with an excess of benzylamine afforded *N*,*N*-dibenzyl derivative **4a**[8] in 93% yield.[9] Benzylamine was also selectively introduced on *C*-5 position of **3**.[9,10] Thus, the reaction of 1 equiv of benzylamine with **3** was carried out at −15 °C to afford **5**[11] in 90% yield. 1,2,4-Triazines **4b–f**[12] were obtained in 57% to 96% yields (Table 1) by treatment of **5** and various amines R^1R^2NH (2 equiv) in dioxane at reflux overnight.

At this point, the Sonogashira cross-coupling reaction[13] followed by heteroannulation on model derivative **4a** (pent-1-yne, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 50 °C) in a one pot reaction was investigated (Scheme 3). In our hands, attempts to obtain **7a** from **4a** were not efficient. Prolonged reaction times or elevated temperatures provided always a mixture of desired product **7a** and acetylenic intermediate **6a**. Cyclized compound was obtained with an optimum yield when a two step procedure was performed. Thus, derivatives **4a–f** were first submitted to Sonogashira reaction in the presence of pent-1-yne, $PdCl_2(PPh_3)_2$ (10 mol %) and CuI (10 mol %) for 5 h at 50 °C. The mixture was then concentrated in vacuo and the crude intermediates **6a–f** were refluxed in MeOH/Et_3N solution (3:1) with a catalytic amount of CuI for 3 h. By this way, compounds **7a–f**[14] were isolated in 62–82% yields (typically 0.3 mmol scale, Table 2). Exemplification of the method was carried out (Sonogashira reaction then Cu-mediated cyclization) on **4a** with miscellaneous alkynes (*N*,*N*-dimethylamino-prop-1-yne, phenylethyne, 4-tetrahydropyran-2-yloxy-but-1-yne and (trimethylsilyl)ethyne) to afford **7g–i** in fair yields (Table 2). It should be noted that the silyl group does not tolerate the cyclization reaction conditions. In this case, a complex mixture of silylated and desilylated derivatives was obtained (not separable by column chromatography). Iodocyclization of **6a** was investigated to reach 7-iodopyrrolo[2,3-*e*]-1,2,4-triazine derivative. Unfortunately, in our hands, attempts (e.g., I_2, $CHCl_3$, room temperature) led to the degradation of the starting material.

Table 1. Synthesis of compounds **4a–f**

R^1R^2NH	R^1	R^2	**4**—Yield[a] (%)
$BnNH_2$	H	Bn	**4a**—93
Morpholine	–$(CH_2)_2$–O–$(CH_2)_2$–		**4b**—89
Cyclopropylamine	H	Cyclopropyl	**4c**—92
Pyrrolidine	–$(CH_2)_4$–		**4d**—96
4-MeO–$C_6H_4NH_2$	H	4-MeO–Ph	**4e**—91
PhNHMe	Me	Ph	**4f**—57

[a] Isolated yield.

Table 2. Synthesis of compounds **7a–i**

R^1	R^2	R^3	**7**—Yield[a] (%)
H	Bn	Propyl	**7a**—77
–$(CH_2)_2$–O–$(CH_2)_2$–		Propyl	**7b**—73
H	Cyclopropyl	Propyl	**7c**—82
–$(CH_2)_4$–		Propyl	**7d**—71
H	4-MeO–Ph	Propyl	**7e**—71
Me	Ph	Propyl	**7f**—62
H	Bn	–CH_2–$N(Me)_2$	**7g**—67
H	Bn	Ph	**7h**—72
H	Bn	–CH_2–O–THP	**7i**—50
H	Bn	$SiMe_3$	—[b]

[a] Isolated yield.
[b] Complex mixture (not separable).

In summary, the Sonogashira/copper(I)-catalyzed heteroannulation sequence was developed to convert 3,5-diamino-6-chloro-1,2,4-triazines to the 6-substituted 3-amino-5*H*-pyrrolo[2,3-*e*]-1,2,4-triazine derivatives. The method described here provides an efficient route to obtain the 5*H*-pyrrolo[2,3-*e*]-1,2,4-triazine scaffold. Further investigation on base-mediated cyclization of **6** will be reported in due course.

Acknowledgement

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8. Compound **4a**: solid. Mp 142–144 °C (EtOH), IR (KBr) *v* 3405, 3240, 3185, 3070, 1615, 1555, 1420, 1340, 1275, 1140, 1060, 745, 716, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.38 (br s, 2H, CH_2Bn), 4.50 (d, 2H, $J = 5.6$ Hz, CH_2Bn), 7.19–7.26 (m, 10H, H_{Ar}), 7.76 (br s, 1H, NH), 8.28 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 43.1 (CH_2), 44.0 (CH_2), 126.6 (CH), 126.9 (CH), 127.2 (2CH), 127.4 (2CH), 128.1 (2CH), 128.3 (2CH), 133.0 (C), 138.6 (C), 140.1 (C), 151.1 (C), 160.6 (C); HRMS (EI) for $C_{17}H_{16}ClN_5$, Calcd: 325.1094. Found: 325.1094.
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11. Compound **5**: To a solution of 3,5,6-trichloro-1,2,4-triazine **3** (353 mg, 1.91 mmol) and Et_3N (0.32 mL, 1.2 equiv) in THF (19 mL) was added dropwise benzylamine (0.21 mL, 1.02 equiv) at −15 °C. The solution was stirred for 30 min at this temperature and warmed to 0 °C for 2 h. After completion of the reaction, solids were removed by filtration and the filtrate concentrated in vacuo. The crude product was then recrystallized from EtOH to give pure **5** (439 mg, 90%) as a solid. Mp 136–137 °C (EtOH); IR (KBr) *v* 3220, 3160, 3080, 2975, 1600, 1495, 1370, 1255, 1200, 1050, 930 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, 2H, $J = 5.6$ Hz, CH_2Bn), 6.15 (br s, 1H, NH), 7.34–7.44 (m, 5H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.4 (CH_2), 128.3 (2CH), 128.5 (CH), 129.1 (2CH), 135.7 (C), 142.8 (C), 152.3 (C), 161.8 (C); HRMS (EI) for $C_{10}H_8Cl_2N_4$, Calcd: 254.0126. Found: 254.0127.
12. Compound **4b**: A solution of **5** (182 mg, 0.71 mmol) and morpholine (0.25 mL, 4 equiv) in THF (7 mL) was heated at reflux overnight. After removing the solids, the filtrate was concentrated in vacuo. The residue was purified by column chromatography (PE/EtOAc 1:1) to give **4b** (194 mg, 89%) as a solid. Mp 145–146 °C (EtOH); IR (KBr) *v* 3280, 3085, 3035, 2955, 2860, 1580, 1530, 1500, 1450, 1275, 1250, 1120, 950, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73–3.79 (m, 8H, CH_2), 4.63 (d, 2H, $J = 5.7$ Hz, CH_2Bn), 5.80 (br s, 1H, NH), 7.30–7.41 (m, 5H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.2 ($2CH_2$), 44.6 (CH_2Bn), 66.7 ($2CH_2$), 127.7 (2CH), 127.9 (CH), 128.8 (2CH), 134.0 (C), 137.2 (C), 151.1 (C), 159.9 (C); HRMS (EI) for $C_{14}H_{16}ClN_5O$, Calcd: 305.1043. Found: 305.1045. Compound **4c**: solid. Mp 147–148 °C (EtOH); IR (KBr) *v* 3420, 3330, 3065, 3000, 1620, 1545, 1510, 1340, 1120, 770, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.52–0.58 (m, 2H, CH_2), 0.76–0.82 (m, 2H, CH_2), 2.71–2.80 (m, 1H, CH), 4.65 (d, 2H, $J = 5.8$ Hz, CH_2Bn), 5.41 (br s, 1H, NH), 5.87 (br s, 1H, NH), 7.31–7.36 (m, 5H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.3 ($2CH_2$), 24.0 (CH), 44.5 (CH_2Bn), 128.0 (3CH), 128.9 (2CH), 134.4 (C), 137.3 (C), 151.6 (C), 161.8 (C); HRMS (EI) for $C_{13}H_{14}ClN_5$, Calcd: 275.0938. Found: 275.0937.
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14. Compound **7a**: To a solution of **4a** (127 mg, 0.39 mmol), CuI (6 mg, 10 mol %) and $PdCl_2(PPh_3)_2$ (27 mg, 10 mol %) in DMF (0.65 mL) was added Et_3N (0.22 mL, 4 equiv) and pent-1-yne (0.19 mL, 5 equiv). The mixture was stirred at 50 °C for 5 h and concentrated in vacuo. The crude product was then refluxed with CuI (7.6 mg, 10 mol %) in MeOH/Et_3N (3.6 mL, 7/3 v/v) for 3 h. Solvents were removed in vacuo and the residue purified by column chromatography (PE/EtOAc 1:1) to give **7a** (107 mg, 77%) as a solid. Mp 150–151 °C; IR (KBr) *v* 3230, 3030, 2960, 1600, 1525, 1410, 1080, 765, 725, 700 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.91 (t, 3H, $J = 7.3$ Hz, CH_3), 1.59 (hex, 2H, $J = 7.3$ Hz, CH_2), 2.58 (t, 2H, $J = 7.3$ Hz, CH_2), 4.54 (d, 2H, $J = 6.2$ Hz, CH_2Bn), 5.26 (s, 2H, CH_2Bn), 6.44 (s, 1H, CH_{Ar}), 7.05–7.08 (m, 2H, H_{Ar}), 7.18–7.34 (m, 8H, H_{Ar}), 7.82 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 13.6 (CH_3), 20.3 (CH_2), 28.0 (CH_2), 43.5 (CH_2Bn), 44.2 (CH_2Bn), 96.9 (CH), 126.5 (CH), 126.7 (2CH), 127.3 (2CH), 127.4 (CH), 128.1 (2CH), 128.7 (2CH), 137.2 (C), 140.4 (C), 140.9 (C), 144.1 (C), 145.2 (C), 159.1 (C); HRMS (EI) for $C_{22}H_{23}N_5$, Calcd: 357.1953. Found: 357.1951. Compound **7b**: amorphous solid; IR (KBr) *v* 3085, 3030, 2960, 2840, 1605, 1500, 1415, 1350, 1260, 1245, 1105, 1085, 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3H, $J = 7.4$ Hz, CH_3), 1.66 (hex, 2H, $J = 7.4$ Hz, CH_2), 2.52 (t, 2H, $J = 7.4$ Hz, CH_2), 3.79–3.87 (m, 8H, CH_2), 5.26 (s, 2H, CH_2Bn), 6.43 (s, 1H, CH_{Ar}), 7.05–7.07 (m, 2H, H_{Ar}), 7.21–7.33 (m, 3H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (CH_3), 20.6 (CH_2), 28.9 (CH_2), 44.2 (CH_2Bn), 44.7 ($2CH_2$), 66.8 ($2CH_2$), 97.8 (CH), 126.6 (2CH), 127.7 (CH), 128.8 (2CH), 136.8 (C),

141.7 (C), 144.8 (C), 146.3 (C), 158.9 (C); HRMS (EI) for $C_{19}H_{23}N_5O$, Calcd: 337.1903. Found: 337.1905. Compound **7c**: amorphous solid; IR (KBr) v 3210, 3080, 2960, 1600, 1520, 1385, 1090, 770,700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.60 (br s, 2H, CH_2), 0.79–0.87 (m, 2H, CH_2), 0.98 (t, 3H, $J = 7.4$ Hz, CH_3), 1.69 (hex, 2H, $J = 7.4$ Hz, CH_2), 2.56 (t, 2H, $J = 7.4$ Hz, CH_2), 2.78–2.88 (m, 1H, CH), 5.28 (s, 2H, CH_2Bn), 6.08 (br s, 1H, NH), 6.44 (s, 1H, H_{Ar}), 7.11–7.14 (m, 2H, H_{Ar}), 7.26–7.31 (m, 3H, H_{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.4 ($2CH_2$), 13.9 (CH_3), 20.6 (CH_2), 24.1 (CH), 29.1 (CH_2), 44.7 (CH_2Bn), 98.3 (CH) 127.0 (2CH), 128.1 (CH), 129.0 (2CH), 136.3 (C), 141.3 (C), 145.8 (C), 148.4 (C), 158.9 (C); HRMS (EI) for $C_{18}H_{21}N_5$, Calcd: 307.1797. Found: 307.1799.