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Selective bifunctionalization of pyrido[2,3-*d*]pyrimidines in positions 2 and 4 by SN_{Ar} and palladium-catalyzed coupling reactions

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Abstract—Selective disubstitution of 2,4-dichloropyrido[2,3-*d*]pyrimidine with various nucleophiles was investigated. Suzuki and Stille cross-coupling reactions on monosubstituted compound 4-*tert*-butylamino-2-chloro-pyrido[2,3-*d*]pyrimidine were performed in high yields.

Pyrido[2,3-*d*]pyrimidines are known to be pharmacophoric elements in numerous active compounds such as anticancer,[1–3] anti-viral,[4,5] and anti-inflammatory agents.[6]

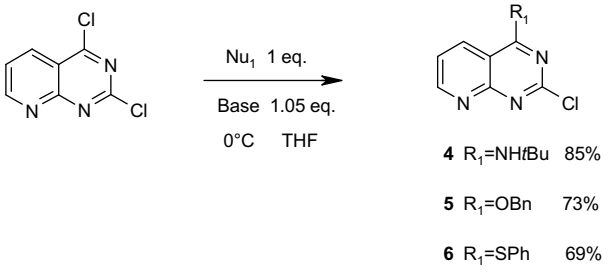
Many publications are devoted to the synthesis of polysubstituted[7,8] and fused pyrido[2,3-*d*]pyrimidine[9,10] system, most whose involve substitution on a pyridine ring.[11,12] Prior exploration on the reactivity of pyrimidine moiety has shown that substitution essentially occurred at position 4.[13]

Aiming to extend pyrido[2,3-*d*]pyrimidine libraries, a useful pathway has been developed to obtain pyrido[2,3-*d*]pyrimidines, that are selectively substituted in positions 2 and 4 with various nucleophiles.

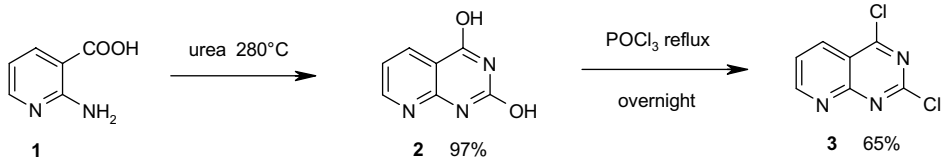
We also describe two types of palladium-mediated cross-coupling reactions (Suzuki and Stille) in position 4, leading to new dissymmetrical species.

Starting material: 2,4-dichloropyrido[2,3-*d*]pyrimidine **3** was prepared from 2-aminonicotinic acid **1** via 2,4-dihydroxypyrido[2,3-*d*]pyrimidine **2** following Robin and Hitchings method[14] (Scheme 1).

Compound **3** was easily substituted at position 4 with different nucleophiles[15] (Scheme 2). This position was more reactive than position 2, as in simple pyrimidinic systems.[16] The structures were confirmed by NOESY studies.



Scheme 2.



Scheme 1. Previous synthesis of 2,4-dichloropyrido[2,3-*d*]pyrimidine **3**.

Keywords: Suzuki reaction; Stille reaction; Cross-coupling; Palladium; SN_{Ar}; Pyrido[2,3-*d*]pyrimidine.
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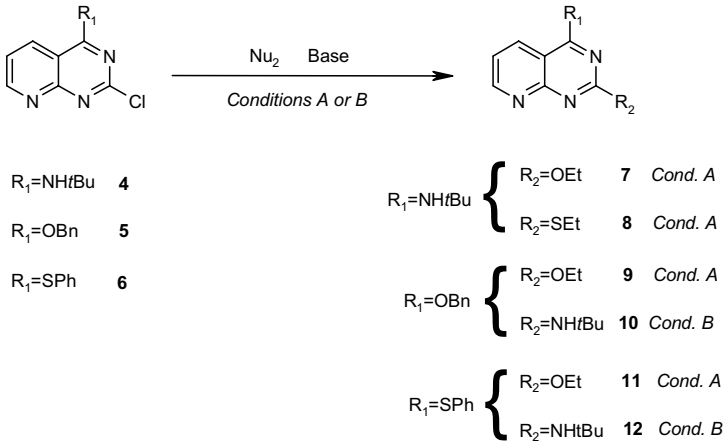


Scheme 3. Reagents and conditions: (A) 1 equiv nucleophile, 1.05 equiv NaH, THF, 0 °C; (B) large excess *tert*-butylamine, THF, reflux overnight.

The reactions proceeded in good yield with high selectivity for position 4, without an isomer in position 2.

The chlorine at position 2 of monosubstituted compounds **4**–**6** could be substituted with several other nucleophiles[17] to give products **7**–**12** as shown in Scheme 3.

The introduction of a *tert*-butylamino-group required harsher conditions than for other nucleophiles such as sodium ethoxide or sodium ethanethiolate, although expected products were obtained in high yield (Table 1).

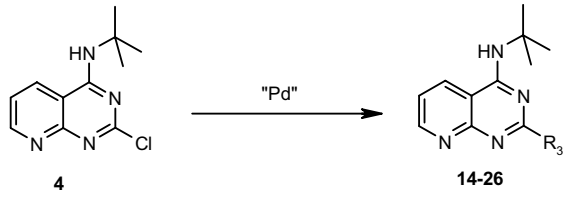
We also found that compounds **9** and **11** were easily substituted at position 4 by sodium ethoxide under very mild conditions, affording **13**[18] (Scheme 4). It should be noted that compound **7** (*tert*-butylamino-group in position 4) did not react even under stringent conditions.

Table 1. Nucleophilic substitutions at position 4

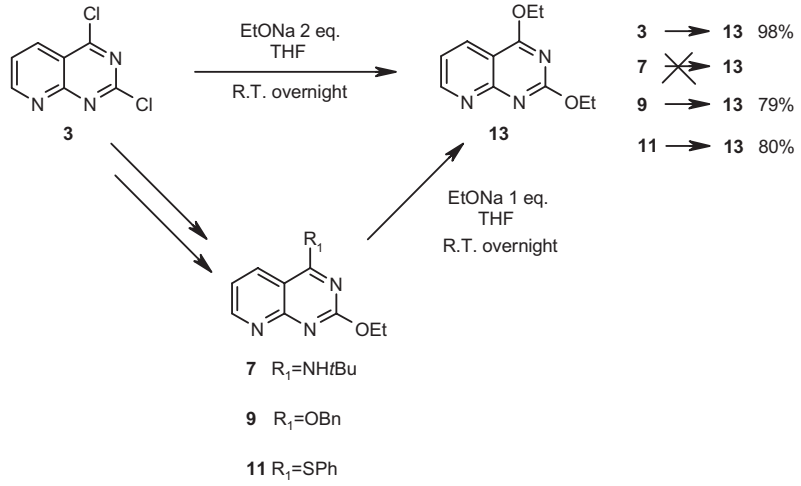
R_1	R_2	Yield (%)
NH-*t*-Bu	OEt	78
	SEt	75
OBn	NH-*t*-Bu	81
	OEt	72
SPh	NH-*t*-Bu	83
	OEt	77

A similar reactivity was already observed with the pyrido[4,3-*d*]pyrimidine system, as methylsulfanyl- or anilino-groups in position 4 were also displaced by nucleophiles.[13]

Position 2 was also functionalized using palladium-promoted cross-coupling reactions performed on compound **4**. Suzuki[19] and Stille[20] conditions were applied (Scheme 5). Unfortunately, the chlorine in position

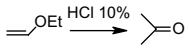
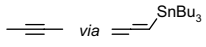


Scheme 5. Suzuki conditions: boronic acid 1.05 equiv, $Pd(PPh_3)_4$ 5 mol%, Na_2CO_3 2 equiv, DME/H_2O, 75 °C. Stille conditions: tin derivative 1.25 equiv, $Pd(PPh_3)_4$ 5 mol%, toluene reflux then TBAF 1 M/THF.



Scheme 4.

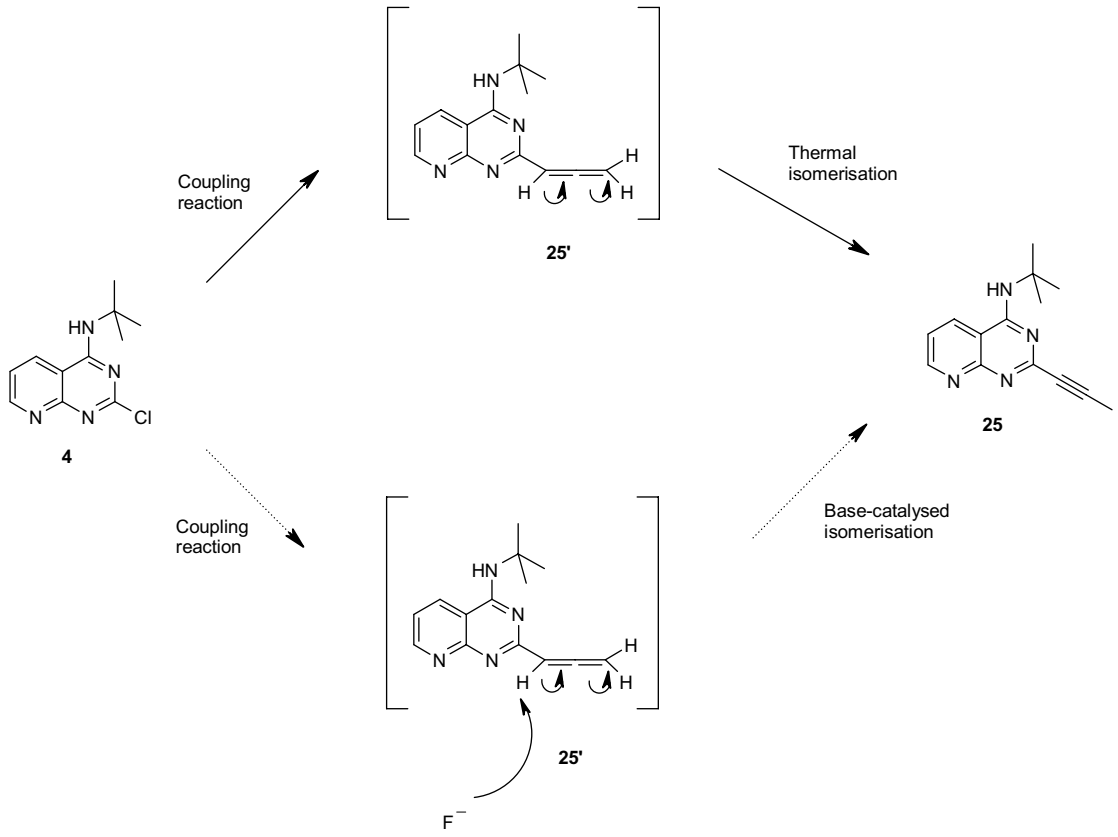
Table 2. Cross-coupling yields

Reaction type	R_3	Reaction time	Yield (%)	Compd
Suzuki coupling	Ph	10 min	92	**14**
	o-MeOPh	1 h	90	**15**
	m-MeCOPh	1 h	89	**16**
	1-Naphtyl	1 h	88	**17**
	4-Pyridyl	12 h	86	**18**
	2-Furyl	2 h	90	**19**
	2-Thiophenyl	4 h	80	**20**
	3-Thiophenyl	4 h	84	**21**
Stille coupling	Ph	1 h	80	**14**
	2-Furyl	1 h	70	**19**
	2-Thiophenyl	6 h	68	**20**
		Coupling: 1 h	71	**22**
		Deprotection: 5 min	100	**23**
		1 h	82	**24**
		3 h	72	**25**
	Me	1 h	78	**26**

2 did not react under the Sonogashira or Heck protocols.

The transformation proceeded under quite mild conditions and reaction times were often short. The experiments led to the expected compounds in excellent yields (Table 2) even for ethoxyvinyl product **22**, of which derivatives are usually sensitive.

The Suzuki and Stille coupling for different R_3 groups are summarized in Table 2. Interestingly, Stille coupling with allenic tin derivatives afforded alkyne **25**, which is unreachable by the Sonogashira method in the present case. Formation of **25** could be explained by a rapid thermal isomerization of allenic intermediate **25′** produced just after the cross-coupling. The possibility of a base-catalyzed isomerization of **25′** with fluoride anion



Scheme 6.

from TBAF workup is less likely since compound **25** was also observed without this workup (Scheme 6).

To resume, disubstituted-pyrido[2,3-*d*]pyrimidines were prepared by the means of easy and clean reactions. Positions 2 and 4 were diversified by introduction of various nucleophiles. Two typical cross-coupling palladium-mediated reactions were successfully investigated from 4-*tert*-butylamino-2-chloro-pyrido[2,3-*d*]pyrimidine. In this way, a new alkyne species **25** was obtained.

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15. General procedure for synthesis of 4-chloro-2-substituted-pyrido[2,3-*d*]pyrimidines **4**–**6**: 5 mmol (1 equiv) of 2,4-dichloropyrido[2,3-*d*]pyrimidine **3** were dissolved in THF (50 mL) then cooled at 0 °C. A solution of 1 equiv nucleophile and 1.05 equiv of sodium hydride (for thiophenol or benzyl alcohol as nucleophile) or 1.05 equiv of triethylamine (for *tert*-butylamine as nucleophile) in THF (15 mL) was added dropwise at 0 °C. The mixture was stirred overnight then 10 mL of cold water was poured onto, and then extracted with ethylacetate. The organic phase wad dried on $MgSO_4$ and finally evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography.
Compound **4**: 4-*tert*-butylamino-2-chloropyrido[2,3-*d*]-pyrimidine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 1.59 (s; 9H; NHCCH_3); 2.04 (s; 3H; CCH_3); 6.05 (sl; 1H; N*H*); 7.28 (dd; 1H; H_6; $J = 4.4$ Hz; $J = 7.8$ Hz); 8.21 (dd; 1H; H_5; $J = 1.5$ Hz; $J = 7.8$ Hz); 8.95 (dd; 1H; H_7; $J = 1.5$ Hz; $J = 4.4$ Hz); ^{13}C NMR ($CDCl_3$) δ_{ppm}: 28.0 (*C*H_3); 53.4 (*C*CH_3); 109.0 (C_{4a}); 121.3 (C_6); 133.7 (C_5); 155.9 (C_7); 158.7; 159.2; 161.3 (C_{8a}); MS: $m/z = 235$ (M+H; ^{35}Cl)$^+$; 237 (M+H; ^{37}Cl)$^+$.
Compound **5**: 4-benzyloxy-2-chloro-pyrido[2,3-*d*]pyrimidine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 5.65 (s; 2H; O*C*H_2Ph); 7.35–7.52 (m; 6H; H_{arom} and H_6); 8.50 (dd; 1H; H_5; $J = 2.0$ Hz; $J = 8.1$ Hz); 9.12 (dd; 1H; H_7; $J = 2.0$ Hz; $J = 4.4$ Hz); ^{13}C NMR δ_{ppm}: 70.6 (O*C*H_2Ph); 110.2 (C_{4a}); 122.8 (C_6); 128.5; 128.8; 128.9; 133.7; 134.7; 157.9 (C_7); 159.6; 160.3; 168.4 (C_4); MS: $m/z = 272$ (M+H; ^{35}Cl)$^+$; 274 (M+H; ^{37}Cl)$^+$.
Compound **6**: 2-chloro-4-phenylsulfanyl-pyrido[2,3-*d*]pyrimidine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 7.48–7.63 (m; 6H; H_{arom} and H_6); 8.55 (dd; 1H; H_5; $J = 1.8$ Hz; $J = 8.3$ Hz); 9.19 (dd; 1H; H_7; $J = 1.8$ Hz; $J = 4.4$ Hz); ^{13}C NMR δ_{ppm}: 118.2(C_{4a}); 124.6 (C_6); 127.0 (C_{arom}); 131.2 (C_{arom}); 132.0 (C_5); 134.9 (C_{arom}); 137.1 (C_{arom}); 159.4; 160.1 (C_7); 161.3; MS: $m/z = 274$ (M+H; ^{35}Cl)$^+$; 276 (M+H; ^{37}Cl)$^+$.
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17. Experimental details of conditions A: 0.35 mmol (1 equiv) of 2-chloro-4-substituted-pyrido[2,3-*d*]pyrimidine were dissolved in THF (20 mL) then cooled at 0 °C. A solution of 1 equiv nucleophile and 1.05 equiv of sodium hydride in THF (5 mL) was added dropwise at 0 °C. The mixture was stirred overnight then the solvents were removed under vacuum. The crude residue was purified by silica gel column chromatography.
Compound **11**: 2-ethoxy-4-phenylsulfanyl-pyrido[2,3-*d*]pyrimidine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 1.36 (t; 3H; CH_2CH_3; $J = 7.0$ Hz); 4.41 (q; 2H; CH_2CH_3; $J = 7.0$ Hz); 7.31 (dd; 1H; H_6; $J = 4.6$ Hz; $J = 8.2$ Hz); 7.40–7.43 (m; 3H; H_{arom}); 7.67–7.72 (m; 2H; H_{arom}); 8.35 (dd; 1H; H_5; $J = 2.0$ Hz; $J = 8.2$ Hz); 8.98 (dd; 1H; H_7; $J = 2.0$ Hz; $J = 4.6$ Hz); ^{13}C NMR ($CDCl_3$) δ_{ppm}: 12.0 (CH_2CH_3); 62.0 (CH_2CH_3); 107.3 (C_{4a}); 119.0 (C_6); 126.9 (C_{arom}); 127.1 (C_{arom}); 127.5 (C_{arom}); 131.3 (C_5); 133.4 (C_{arom}); 154.8 (C_7); 158.0 (C_4); 164.5 (C_{8a}); 169.6 (C_2); MS: $m/z = 284$ (M+H)$^+$.
Experimental details of conditions B: 0.37 mmol (1 equiv) of 2-chloro-4-substituted-pyrido[2,3-*d*]pyrimidine were dissolved in THF (20 mL) then excess of *tert*-butylamine (2 mL) was added, and the mixture was refluxed overnight. After cooling, the solvents were evaporated under vacuum. The crude residue was purified by silica gel column chromatography. Compound **12**: 2-*tert*-butyl-amino-4-phenylsulfanyl-pyrido[2,3-*d*]pyrimidine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 1.57 (s; 9H; CCH_3); 7.08 (dd; 1H; H_6; $J = 4.4$ Hz; $J = 8.1$ Hz); 7.44–7.46 (m; 3H; H_{arom}); 7.57–7.60 (m; 2H; H_{arom}); 8.26 (dd; 1H; H_5; $J = 1.8$ Hz; $J = 8.1$ Hz); 8.86 (dd; 1H; H_7; $J = 1.8$ Hz; $J = 4.4$ Hz); ^{13}C NMR δ_{ppm}: 28.9 (C*C*H_3); 51.2 (*C*CH_3); 117.2 (C_{4a}); 120.8 (C_6); 127.3; 129.2; 129.5; 129.8; 133.2; 156.0 (C_7); 157.3; MS: $m/z = 311$ (M+H)$^+$.
18. Preparation of **13**. 0.5 mmol (1 equiv) of **9** or **11** were dissolved in THF (20 mL), then a solution of ethanol (1 equiv), and sodium hydride (1.05 equiv) in THF (5 mL) was added. The mixture was stirred overnight, then the solvents were removed under reduced pressure. The crude residue was purified by silica gel column chromatography (dichloromethane/ethylacetate 5/5).
Compound **13**: 2,4-diethoxy-pyrido[2,3-*d*]pyrimidine: ^{1}H NMR ($CDCl_3$) δ_{ppm}: 1.47–1.54 (m; 6H; CH_2CH_3); 4.60–4.70 (m; 4H; CH_2CH_3); 7.31 (dd; 1H; H_6; $J = 4.4$ Hz; $J = 7.9$ Hz); 8.40 (dd; 1H; H_5; $J = 2.2$ Hz; $J = 7.9$ Hz);

8.98 (dd; 1H; H_7; $J = 2.2$ Hz; $J = 4.4$ Hz); ^{13}C NMR δ_{ppm}: 14.2 (CH_2CH_3); 14.4 (CH_2CH_3); 64.1 ($2 \times CH_2CH_3$); 108.4 (C_{4a}); 119.8 (C_6); 133.5 (C_5); 156.6 (C_7); 161.0 (C_{8a}); 164.2 (C_2 or C_4); 169.4 (C_2 or C_4); MS: $m/z = 220$ $(M+H)^+$.

19. See experimental section for Suzuki coupling: Enguehard, C.; Renou, J. L.; Allouchi, H.; Leger, J. M.; Gueiffier, A. *Chem. Pharm. Bull.* **2000**, *48*, 935–940.
Compound **16**: 4-*tert*-butylamino-2-(*m*-methylcarbonylphenyl)-pyrido[2,3-*d*]pyrimidine: ^1H NMR ($CDCl_3$) δ_{ppm}: 1.70 (s; 9H; NHCCH_3); 2.70 (s; 3H; COCH_3); 6.45 (sl; 1H; N*H*); 7.28 (dd; 1H; H_6; $J = 4.2$ Hz; $J = 8.0$ Hz); 7.45–7.70 (m; 2H; H_{arom}); 8.09–8.12 (m; 1H; H_{arom}); 8.38 (dd; 1H; H_5; $J = 1.6$ Hz; $J = 8.0$ Hz); 8.84–8.87 (m; 1H; H_{arom}); 8.98 (dd; 1H; H_7; $J = 1.6$ Hz; $J = 4.2$ Hz); ^{13}C NMR δ_{ppm}: 26.8 (CO*C*H_3); 28.8 (NHC*C*H_3); 53.3 (NH*C*CH$_3$); 109.2 (C_{4a}); 120.7 (C_6); 128.6; 129.3; 129.9; 131.1; 133.4; 137.2; 139.0; 155.6 (C_7); 159.4; 160.2; 162.3; 198.5 (*C*=O); MS: $m/z = 265$ $(M+H-t\text{-Bu})^+$, 321 $(M+H)^+$; IR (cm^{-1}, KBr): 1685 (C=O).
Compound **19**: 4-*tert*-butylamino-2-(furan-2-yl)-pyrido[2,3-*d*]pyrimidine: ^1H NMR ($CDCl_3$) δ_{ppm}: 1.59 (s; 9H; CH_3); 6.01 (sl; 1H; N*H*); 6.54 (dd; 1H; H_{fur}; $J = 1.8$ Hz; $J = 3.4$ Hz); 7.25 (dd; 1H; H_6; $^3J = 4.4$ Hz; $^3J = 8.1$ Hz); 7.39 (dd; 1H; H_{fur}; $J = 0.8$ Hz; $J = 3.4$ Hz); 7.60 (dd; 1H; H_{fur}; $J = 0.8$ Hz; $J = 1.8$ Hz); 8.18 (dd; 1H; H_5; $J = 1.8$ Hz; $J = 8.1$ Hz); 8.93 (dd; 1H; H_7; $J = 1.8$ Hz; $J = 4.4$ Hz); ^{13}C NMR ($CDCl_3$) δ_{ppm}: 28.8 (C*C*H$_3$); 53.3 (*C*CH$_3$); 109.0 (C_{4a}); 112.0 (C_{fur}); 114.1 (C_{fur}); 120.3 (C_6); 130.6 (C_5); 145.0 (C_{fur}); 153.3 (C_{fur}); 155.6 (C_7); 156.4 (C_4); 159.4 (C_2 or C_{8a}); 160.1 (C_2 or C_{8a}); MS: $m/z = 213$ $(M+H-t\text{-Bu})^+$, 269 $(M+H)^+$.

20. See experimental section for Stille coupling: Aboul-Fadl, T.; Löber, S.; Gmeiner, P. *Synthesis* **2000**, 1727–1732Compound **24**: 4-*tert*-butylamino-2-vinyl-pyrido[2,3-*d*]pyrimidine: ^1H NMR ($CDCl_3$) δ_{ppm}: 1.62 (s; 9H; CH_3); 5.71–5.81 (m; 2H; CH=CH_2); 6.66–6.95 (m; 2H; C*H*=CH$_2$ and H_6); 8.10 (sl; 1H; H_5); 8.93 (sl; 1H; H_7); ^{13}C NMR ($CDCl_3$) δ_{ppm}: 29.1 (*C*H$_3$); 53.6 (*C*CH$_3$); 109.4 (C_{4a}); 120.9 (C_6); 124.4 (CH=*C*H$_2$); 130.7 (C_5); 138.5 (*C*H=CH$_2$); 155.8 (C_7); 159.7 (C_2 or C_4); 160.0 (C_2 or C_4); 163.7 (C_{8a}); MS: $m/z = 173$ $(M+H-t\text{-Bu})^+$, 229 $(M+H)^+$.
Compound **25**: 4-*tert*-butylamino-2-(methylethynyl)-pyrido[2,3-*d*]pyrimidine: ^1H NMR ($CDCl_3$) δ_{ppm}: 1.59 (s; 9H; NHCCH_3); 2.04 (s; 3H; C≡CCH_3); 6.05 (sl; 1H; N*H*); 7.28 (dd; 1H; H_6; $J = 4.4$ Hz; $J = 7.8$ Hz); 8.21 (dd; 1H; H_5; $J = 1.5$ Hz; $J = 7.8$ Hz); 8.95 (dd; 1H; H_7; $J = 1.5$ Hz; $J = 4.4$ Hz); ^{13}C NMR ($CDCl_3$) δ_{ppm}: 4.5 (C≡C*C*H$_3$); 28.8 (NC*C*H$_3$); 53.5 (NH*C*CH$_3$); 81.0 (C≡*C*CH$_3$); 84.4 (*C*≡CCH$_3$); 109.3 (C_{4a}); 120.9 (C_6); 130.7 (C_5); 151.3 (C_7); 152.1; 158.9; 160.1; MS: $m/z = 185$ $(M+H-t\text{-Bu})^+$, 241 $(M+H)^+$.