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Direct C–H amination and C–H chloroamination of 7-deazapurines†

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Protocols for selective Pd–Cu-catalyzed direct C–H amination or C–H chloroamination of 7-deazapurines with *N*-chloro-*N*-alkyl-arylsulfonamides have been developed leading either to 8-(arylsulfonyl)methylamino-7-deazapurines or to 7-chloro-8-(arylsulfonyl)methylamino-7-deazapurines. The scope and limitations of the methods, as well as synthesis of a small series of 6,8,9-tri- and 6,7,8,9-tetrasubstituted 7-deazapurines and deprotection of the sulfonamide are presented.

Introduction

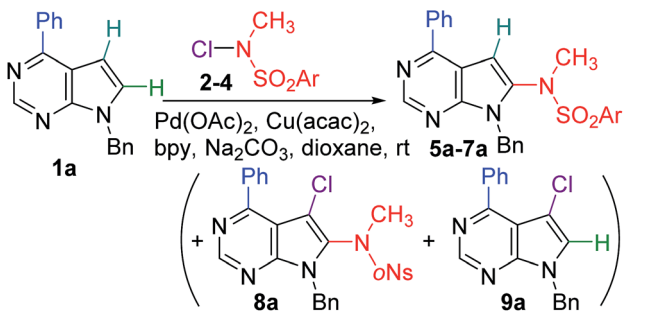
Modified pyrrolo[2,3-*d*]pyrimidine (7-deazapurine)[1] bases and nucleosides display a variety of biological effects. Substituted 7-deazapurine bases induct neurogenesis[2] or exert antitumor[3] or antiinflammatory[4] activity, whereas 6- or 7-aryl-7-deazapurine nucleosides are potent cytostatics.[5,6] Therefore, development of regioselective synthesis of 7-deazapurines bearing multiple substituents is a worthwhile goal. Some regioselective cross-couplings of di- or trihalogenated pyrrolo[2,3-*d*]pyrimidines were recently reported for the synthesis of di- or triaryl derivatives.[7,8] We have developed regioselective C–H borylation[9] and C–H sulfenylation[10] leading to 8-B- or 8-S-substituted 7-deazapurines. Here we report on complementary C–H aminations.

Metal-catalyzed direct C–H aminations are increasingly popular reactions for modifications of arenes and heterocycles.[11–14] One of the most efficient reagents are *N*-chlorosulfonamides under Pd/Cu catalysis.[13] Inspired by related C–H aminations of indoles,[13] we decided to study the C–H aminations of pyrrolo[2,3-*d*]pyrimidines (7-deazapurines). The only previously reported C–H amination of 7-deazapurine was performed through hypervalent iodanes and proceeded at position 7.[14]

Results and discussion

For our initial study, we selected easily accessible 6-phenyl-9-benzyl-7-deazapurine **1a**.[9] We started testing its reaction with *N*-chloro-*N*-methyl-tosylamide **2** under literature[13] conditions in presence of $Pd(OAc)_2$, $Cu(acac)_2$, 2,2′-bipyridine (bpy), Na_2CO_3 in dioxane (Scheme 1 and Table 1). The reaction with 2 equiv. of **2** in presence of 2 equiv. of Na_2CO_3 gave the desired 8-tosylamino product **5a** in 13% only (entry 1). The use of a larger excesses of the base (5–7 equiv.) and of reagent **2** (3 equiv.) led to only low increase of yields (18–29%). Only the use of large excess (5 equiv.) of **2** gave product **5a** in acceptable preparative yields of 68%.

In order to have a choice of some more easily cleavable N-protecting groups,[15] we also tested 4-nitrophenylsulfonyl- (*p*-nosyl, *p*Ns) and 2-nitrophenylsulfonyl (*o*-nosyl, *o*Ns) chloroamides **3** and **4**. The reaction of **1a** with *p*Ns reagent **3** (3 equiv.) gave the 8-*p*-nosylamino product **6a** in acceptable 48% yield (entry 6). The reactions of **1a** with *o*Ns chloroamide **4** (2–3 equiv.) gave very low conversions (see Table S1 in ESI†), whereas the reaction with 5 equiv. of **4** gave a mixture of the desired product of 8-amination **7a** (28%) accompanied by 7-chloro-



Scheme 1 C–H aminations of **1a**.

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Table 1 Optimization of C–H aminations of 7-deazapurine **1a** with *N*-chloro-*N*-methyl-arylsulfoneamides (**2–4**)[a]

Entry	Ar	**2–4** (equiv.)	Na_2CO_3 (equiv.)	Product(s) (yield)
1	4-MePh	**2** (2)	2	**5a** (13%)
2	4-MePh	**2** (2)	5	**5a** (18%)
3	4-MePh	**2** (3)	5	**5a** (25%)
4	4-MePh	**2** (3)	7	**5a** (29%)
5[b]	4-MePh	**2** (5)	7	**5a** (68%)
6	4-NO_2Ph	**3** (3)	7	**6a** (47%)
7	2-NO_2Ph	**4** (5)	5	**7a** (28%) + **8a** (33%) + **9a** (25%)
8	2-NO_2Ph	**4** (3)	7	**7a** (60%)

[a] Reagents and conditions: $Pd(OAc)_2$ (5%), $Cu(acac)_2$ (10%), bpy (10%), Na_2CO_3, 1,4-dioxane, Ar, rt, 24 h. [b] Reaction time 72 h.

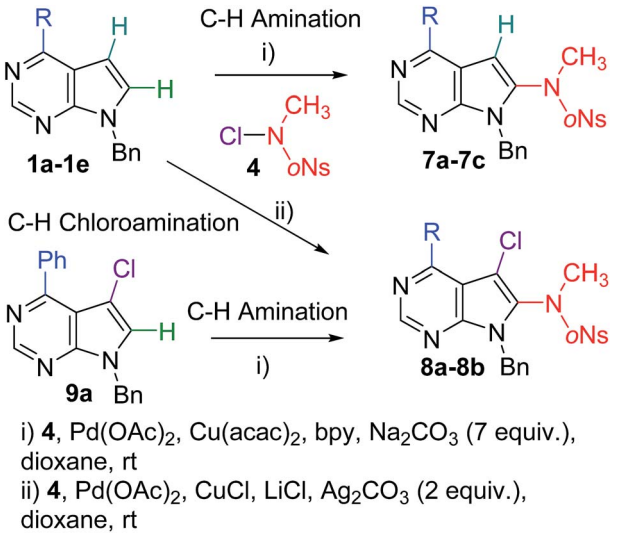
8-amino- **8a** and 7-chloro-7-deazapurine **9a** as side-products. Apparently, the chloroamide **4** in larger excess can act as an electrophilic chlorination reagent which halogenates the deazapurine at position 7 (similarly as it was shown in indoles[13]). Therefore, we performed a detailed optimization of this reaction using different ratios of reagents, catalysts and additives and different conditions (see Table S1 in ESI†). The optimum protocol for aminations used 3 equiv. of **4** in presence of large excess of Na_2CO_3 (7 equiv.) to give the desired product **7a** in 60% yield (Table 1, entry 8).

The detailed optimization also revealed some ratios of reagents and conditions under which the chloroamination proceeds. Also inspired by the related work on indoles,[13] we employed CuCl as copper source, Ag_2CO_3 as base and LiCl as additive (Table S1 in ESI†) to find an optimum protocol leading exclusively to chloroamination,[13,16] employing **4** (3 equiv.) in presence of $Pd(OAc)_2$, CuCl (10 mol%), LiCl (2 equiv.) and Ag_2CO_3 (2 equiv.).

The next step was the study of the scope and limitation of the methods. A series of five 9-benzyl-7-deazapurine derivatives **1a–1e** bearing phenyl, methoxy, methyl, chloro or amino group at position 6 was tested in the amination and chloroamination protocols (Scheme 2 and Table 2). The preparative aminations were performed with choroamide **4** (3 equiv.) in presence of $Pd(OAc)_2$, $Cu(acac)_3$, bpy and 7 equiv. of Na_2CO_3. The reactions of 6-phenyl, -methoxy and -methyl deazapurines proceeded smoothly to give desired 8-(*o*-nosyl)methylamino-7-deazapurines **7a–7c** in acceptable yields of 41–62%. Conversely, analogous reaction of 6-chloro- and 6-amino-derivatives **1d,e** led to very complex inseparable mixtures.

Then we tested the chloroamination protocol on the same series of deazapurines **1a–1e**. The reactions with **4** (3 equiv.) were performed in presence of $Pd(OAc)_2$, CuCl, LiCl and Ag_2CO_3. The reactions of 6-phenyl and 6-methoxy derivatives **1a,b** proceeded well to get desired 7-chloro-8-(*o*Ns)MeNH-7-deazapurines **8a,b** in acceptable yields of 51 and 42%, whereas the reaction of 6-methyl derivative **1c** gave low conversion to inseparable mixture containing products of chlorination and chloroamination. Similarly, the reactions of 6-chloro- and 6-aminodeazapurines **1d,e** gave complex inseparable mixtures. Finally, 6-phenyl-7-chloro-7-deazapurine **9a** was also converted to 7-chloro-8-aminated derivative **8a** in 41% yield showing that the chlorine at position 7 is better tolerated (as it is less reactive toward nucleophiles) than the chlorine at position 6.

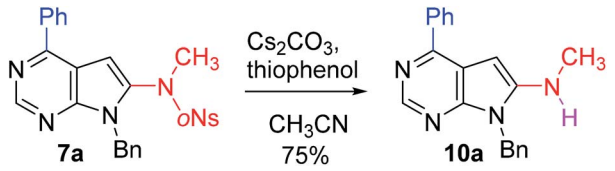
The last goal in this study was to test a deprotection of the sulfonamides and the stability of the corresponding 8-amino-7-deazapurines (2-aminoindoles are prone to tautomerization[17] and oxidation[18]). Any attempt to cleave the Ts- or *p*Ns-groups in



Scheme 2 C–H aminations and chloroaminations of 7-deazapurines.

Table 2 Preparative C–H aminations chloroaminations of 7-deazapurines

Entry	Starting compd	R	Product (yield)
1	**1a**	Ph	**7a** (62%)
2	**1b**	OMe	**7b** (60%)
3	**1c**	Me	**7c** (41%)
4	**1d**	Cl	Complex mixture
5	**1e**	NH_2	Complex mixture
6	**1a**	Ph	**8a** (51%)
7	**1b**	OMe	**8b** (42%)
8	**1c**	Me	Low conversion, complex mixture
9	**1d**	Cl	Complex mixture
10	**1e**	NH_2	Complex mixture
11	**9a**	Ph	**8a** (41%)



Scheme 3 Deprotection of **7a**.

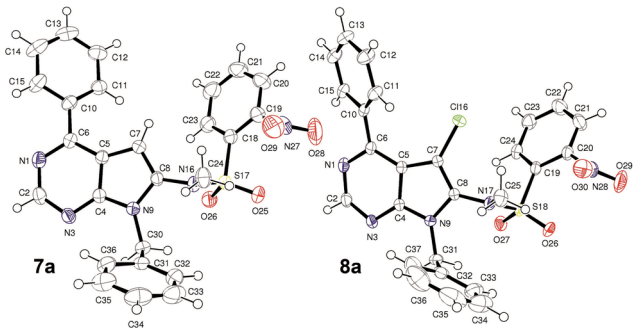


Fig. 1 An ORTEP view of compounds **7a** (CCDC 1014820) and **8a** (1014817) shown with 50% probability displacement ellipsoids. Structures **5a** (1014819) and **7b** (1014818) are shown in ESI.†

compounds **5a** or **6a** according to literature[15] either did not work or led to decomposition of the heterocycles. Therefore, major part of this study was performed with *o*Ns-group which is more easily cleavable.[15] The deprotection of compound **7a** was successfully performed using thiophenol and cesium carbonate[15d] to afford 8-methylamino-7-deazapurine **10a** in 75% yield (Scheme 3). We performed also one-pot C–H amination deprotection sequence to furnish the desired compound **10a** directly in 35% for two steps. The 8-(methylamino)-7-deazapurine **10a** was reasonably stable under neutral conditions but quickly decomposed when exposed to even traces of acid (*e.g.* in chlorinated solvents).

All new compounds were fully characterized by NMR spectroscopy including assignment of all signals. In addition, to confirm the regioselectivity of the reactions, single-crystal X-ray diffraction was performed with compounds **5a**, **7a**, **7b** and **8a**. Fig. 1 shows the crystal structures of compounds **7a** and **8a** (for structures of **5a** and **7b**, see ESI†).

Conclusions

In conclusion, we have developed selective protocols for palladium/copper-catalyzed direct C–H amination and C–H chloroamination of 7-deazapurines with *N*-chloro-*N*-alkyl-arylsulfoneamides. Reactions proceed under mild conditions regioselectively at position 8 of 7-deazapurines (in analogy to aminations at position 2 of indoles[13]) and are applicable to 6-aryl, -alkyl and -alkoxy 7-deazapurine derivatives. On the other hand, they are not compatible with 6-amino- and 6-chloro derivatives. Apart from the potential for the synthesis of series of 8-(arylsulfonyl)methylamino-7-deazapurines (and their 7-chloro-derivatives), when using *o*Ns sulfonamides, the deprotection is possible to 8-methylamino-7-deazapurines. These protocols nicely complement the current toolbox of reactions for modifications of these privileged heterocycles and will be used for generation of libraries of compounds for biological activity screening.

Experimental

General procedure for C–H amination of 7-deazapurines

7-Deazapurine **1a–1e** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), $Cu(acac)_2$ (0.05 mmol), bpy (0.05 mmol), Na_2CO_3 (3.5 mmol) and chlorosulfonamide (1–1.75 mmol) were placed in a vial which was purged with argon. Then 1,4-dioxane (2 mL) was added and the reaction mixture was then stirred for 24 h at rt, then quenched with H_2O (2 mL), extracted with ethyl acetate (3 × 20 mL) and washed with brine (2 mL). The organic phases were combined and dried over sodium sulphate, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel, eluting with hexanes/EtOAc (5 : 1 to 1 : 2) to afford the corresponding product.

N-(7-benzyl-4-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-*N*-methyl-2-nitrobenzenesulfonamide (7a)

1a (285 mg, 1 mmol) and *N*-chloro-*N*-methyl-2-nitrobenzenesulfonamide **4** (877 mg, 3.5 mmol) were used as starting compounds to give product **7a** (310 mg, 62%) as colourless crystals after chromatography with hexanes/EtOAc 5 : 1 to 1 : 1 and crystallization from EtOAc/hexane. M.p. 102–103 °C. ^{1}H NMR (500.0 MHz, $CDCl_3$): 2.94 (s, 3H, CH_3N); 5.67 (bs, 2H, CH_2Ph); 6.45 (s, 1H, H-5); 7.22 (m, 2H, H-*o*-Bn); 7.27 (m, 1H, H-*p*-Bn); 7.30 (m, 2H, H-*m*-Bn); 7.50–7.53 (m, 3H, H-*m*,*p*-Ph); 7.61 (ddd, 1H, $J_{5,6}$ = 8.1, $J_{5,4}$ = 7.5, $J_{5,3}$ = 1.3, H-5-$C_6H_4NO_2$); 7.67 (ddd, 1H, $J_{3,4}$ = 8.0, $J_{3,5}$ = 1.3, $J_{3,6}$ = 0.5, H-3-$C_6H_4NO_2$); 7.76 (ddd, 1H, $J_{6,5}$ = 8.1, $J_{6,4}$ = 1.4, $J_{6,3}$ = 0.5, H-6-$C_6H_4NO_2$); 7.77 (ddd, 1H, $J_{4,3}$ = 8.0, $J_{4,5}$ = 7.5, $J_{4,6}$ = 1.4, H-4-$C_6H_4NO_2$); 7.97 (m, 2H, H-*o*-Ph); 9.10 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 40.53 (CH_3N); 45.29 (CH_2Ph); 96.40 (CH-5); 113.91 (C-4a); 124.12 (CH-3-$C_6H_4NO_2$); 127.65 (CH-*o*-Bn); 127.89 (CH-*p*-Bn); 128.85 (CH-*m*-Ph, CH-*o*-Bn); 128.94 (CH-*m*-Ph); 130.16 (C-1-$C_6H_4NO_2$); 130.64 (CH-*p*-Ph); 131.26 (CH-5-$C_6H_4NO_2$); 132.23 (CH-6-$C_6H_4NO_2$); 134.62 (CH-4-$C_6H_4NO_2$); 136.54 (C-i-Bn); 136.86 (C-i-Ph); 137.04 (C-6); 148.55 (C-2-$C_6H_4NO_2$); 150.56 (C-7a); 152.40 (CH-2); 157.48 (C-4). IR(KBr): 2821, 1545, 1376, 1368, 1360, 1343, 1318, 1309, 1180, 1163, 924. HRMS (ESI) calculated for $C_{26}H_{22}N_5O_4S$: 500.1387; found 500.1387.

General procedure for C–H chloroamination of 7-deazapurines

7-Deazapurine **1a–1e** (0.5 mmol), $Pd(OAc)_2$ (0.0125 mmol), CuCl (0.05 mmol), LiCl (1.0 mmol), Ag_2CO_3 (1.0 mmol) and chlorosulfonamide (1.5–1.75 mmol) were placed in a vial which was purged with argon. Then 1,4-dioxane (2 mL) was added and the reaction mixture was stirred for 24 h at room temperature, then quenched with H_2O (2 mL), extracted with ethyl acetate (3 × 20 mL) and washed with brine (2 mL). The organic phases were combined and dried over sodium sulphate, filtered, and evaporated under vacuum. The crude product was purified by

column chromatography on silica gel, eluting with hexanes/EtOAc (5 : 1 to 1 : 2) to afford the corresponding product.

N-(7-benzyl-5-chloro-4-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl)-*N*-methyl-2-nitrobenzenesulfonamide (8a)

1a (285 mg, 1 mmol) and **4** (877 mg, 3.5 mmol) were used as starting compounds to give product **8a** (273 mg, 51%) as white crystals after chromatography with hexanes/EtOAc 5 : 1 to 1 : 1 and crystallization from EtOAc/hexane. M.p. 215–216 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 2.91 (s, 3H, CH_3N); 5.42 (d, 1H, J_{gem} = 15.3 Hz, CH_2a-Ph); 6.16 (d, 1H, J_{gem} = 15.3 Hz, CH_2b-Ph); 7.26–7.31 (m, 3H, H-*o*,*p*-Bn); 7.33 (m, 2H, H-*m*-Bn); 7.42–7.50 (m, 3H, H-*m*,*p*-Ph); 7.58–7.63 (m, 2H, H-3,5-$C_6H_4NO_2$); 7.71 (m, 2H, H-*o*-Ph); 7.73 (ddd, 1H, $J_{4,3} = J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.4 Hz, H-4-$C_6H_4NO_2$); 7.84 (m, 1H, H-6-$C_6H_4NO_2$); 9.09 (s, 1H, H-2). ^{13}C NMR (125.7 MHz, $CDCl_3$): 38.28 (CH_3–N); 45.68 (CH_2-Ph); 103.08 (C-5); 112.02 (C-4a); 124.00 (CH-3-$C_6H_4NO_2$); 127.84 (CH-*m*-Ph); 128.09 (CH-*p*-Bn); 128.11 (CH-*o*-Bn); 128.95 (CH-*m*-Bn); 129.86 (CH-*p*-Ph); 130.20 (CH-*o*-Ph); 131.45 (CH-5-$C_6H_4NO_2$); 131.62 (C-1-$C_6H_4NO_2$); 131.65 (CH-6-$C_6H_4NO_2$); 131.89 (C-6); 134.49 (CH-4-$C_6H_4NO_2$); 136.48 (C-i-Bn); 136.62 (C-i-Ph); 148.56 (C-2-$C_6H_4NO_2$); 148.78 (C-7a); 153.18 (CH-2); 160.20 (C-4). IR(KBr): 3050, 1583, 1545, 1374, 1345, 1165, 826, 558. HRMS (ESI) calculated for $C_{26}H_{21}N_5O_4SCl$: 534.0998; found: 534.0997.

Acknowledgements

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