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Efficient *N*-Arylation and *N*-Alkenylation of the Five DNA/RNA Nucleobases

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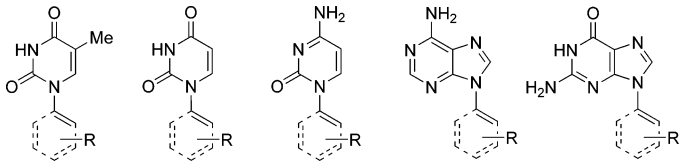

A general approach to *N*-arylation and *N*-alkenylation of all five DNA/RNA nucleobases at the nitrogen atom normally attached to the sugar moiety in DNA or RNA has been developed. Various protected or masked nucleobases engaged readily in the copper-mediated Chan−Lam−Evans-modified Ullmann condensation with a range of different boronic acids at room temperature and were subsequently converted to the corresponding deprotected or unmasked adducts. Different N^3-protecting groups were examined in the case of thymine, where the benzoyl group afforded the highest yields. A 4-alkylthio-substituted pyrimidin-2(1*H*)-one served as both a cytosine and a uracil precursor and was *N*-arylated and *N*-alkenylated in high yields. Adenine was efficiently and selectively *N*-arylated and *N*-alkenylated at the N^9 position by employing a bis-Boc-protected adenine derivative, while a bis-Boc-protected 2-amino-6-chloropurine served as guanine precursor and could also be selectively N^9-arylated and N^9-alkenylated.

Introduction

The ability to modify individual nucleobases is of major importance both in the development of drugs[1] and in the study of nucleic acid function and structure.[2] The interaction between nucleobases in DNA and RNA has been extensively studied in solution and in the solid state,[3] and notably, surface studies using scanning tunneling microscopy have emerged as a means for investigating base pairing in self-assembled structures.[4] Recent efforts have focused on the synthesis and properties of nucleic acid analogues incorporating *N*-aryl-modified nucleobases.[5] These analogues feature a π electron-rich backbone with a bisaryl-like linkage to the nucleobase instead of a natural ribose phosphate (DNA and RNA) or (2-aminoethyl)glycine peptide (PNA) backbone. Furthermore, several *N*-arylpurines and *N*-arylpyrimidines show interesting biological activities, such as agonism and antagonism toward receptors and enzymes as well as antiviral and antibacterial activities.[6] Motivated by this, in

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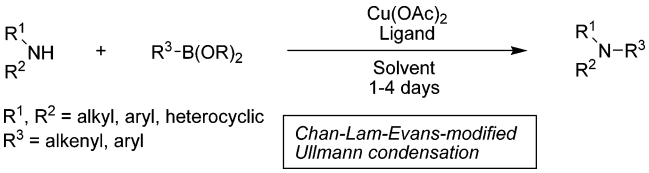
addition to our interest in DNA self-assembled nanostructures[7] and the study of the self-organization of organic molecules on surfaces,[8] we pursued a general route to *N*-aryl and *N*-alkenyl derivatives of all five DNA/RNA nucleobases.

While methods for the synthesis of *N*-alkylpurines and *N*-alkylpyrimidines are well developed,[9] general and efficient methods for the formation of *N*-aryl and *N*-alkenyl analogues are lacking. Classically, the synthesis of *N*-aryl or *N*-alkenyl derivatives of purines has centered on the heterocyclization of suitable precursors, for example, chloropyrimidines, which are often not readily available.[10] In the synthesis of *N*-aryl or *N*-alkenyl derivatives of pyrimidines, the reaction of suitable pyrimidinones with aryliodonium salts has been exploited, both in the case of cytosine[11] and in the case of thymine/uracil;[12] however, low yields of product are generally obtained. Because of their limited scope and the often high temperatures employed (>150 °C), the S_NAr reactions of electron-deficient aryl halides with nucleobases to furnish *N*-aryl nucleobases have only been exploited in a few cases.[13] Dahl and co-workers reported the preparation of *N*-alkenyl nucleobases (enamines) by the Horner−Wadsworth−Emmons reaction of phosphine oxide derivatives of thymine and adenine.[14] However, the basic reaction conditions often resulted in low yields due to enolization and decomposition.

The Chan−Lam−Evans-modified Ullmann condensation has proved to be among the most versatile and mild methods available for C−N bond formation employing boronic acids as aryl or alkenyl donors in the presence of copper species (Scheme 1).[15] Although the reaction has been studied with a plethora of different nitrogen compounds,[16] only a few examples of *N*-arylation of pyrimidines and purines employing the Chan−Lam−Evans reaction have been described, and no examples of *N*-alkenylation have, to the best of our knowledge, been reported.

SCHEME 1. Copper-Mediated C−N Bond Formation Employing Boronic Acids



Schultz and co-workers reported the reaction of 2,6-dichloropurine with arylboronic acids,[17] while Gundersen and Bakkestuen accomplished the regioselective N^9-arylation of various purine structures with arylboronic acids, although attempts with adenine itself were unsuccessful.[18] Yu and co-workers recently described the direct *N*-arylation of adenine and cytosine in an aqueous solution, and although yields were generally good, the low solubility of pure cytosine and adenine in aqueous MeOH demanded a large solvent−substrate ratio.[19] Evidently, the notoriously low solubility of pure nucleobases in many solvents makes their direct manipulation troublesome, and the presence of several amino functionalities could potentially lead to a low regioselectivity in any *N*-arylation and *N*-alkenylation reaction. We envisioned that the use of readily available protected or masked nucleobases in the copper-mediated *N*-arylation and *N*-alkenylation with boronic acids could circumvent any complications due to low solubility and the presence of multiple amino functionalities and could provide a general and facile route to *N*-aryl and *N*-alkenyl derivatives of nucleobases (Scheme 2). The significantly improved solubility of the protected coupling products allows standard chromatographic purification to be carried out. Also, the use of protected or masked nucleobases may prove advantageous in the case of any subsequent transformations of the newly introduced aryl or alkenyl moieties. Our goal was to perform selective *N*-arylation and *N*-alkenylation at the nitrogen atom in the nucleobases which is normally attached to the sugar moiety in DNA or RNA, such that the products may engage in similar base pairing.

Results and Discussion

Initial efforts focused on the *N*-arylation of thymine and on choosing the optimal N^3-protection group. Three different N^3-protection groups were examined, 4-*tert*-butylbenzyl, Boc, and benzoyl (Bz). All three thymine derivatives are readily soluble

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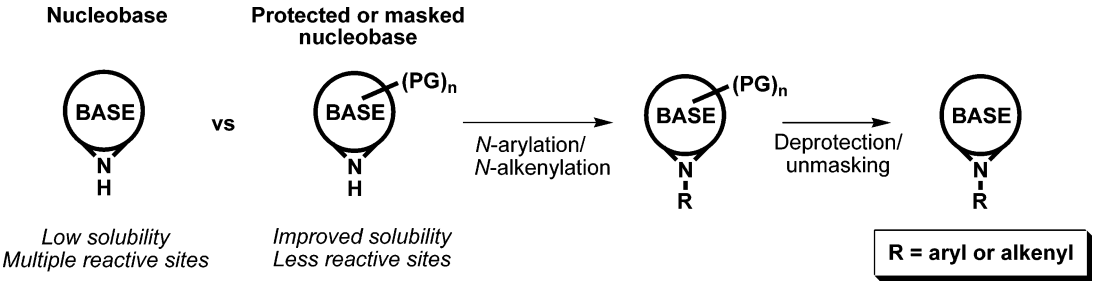
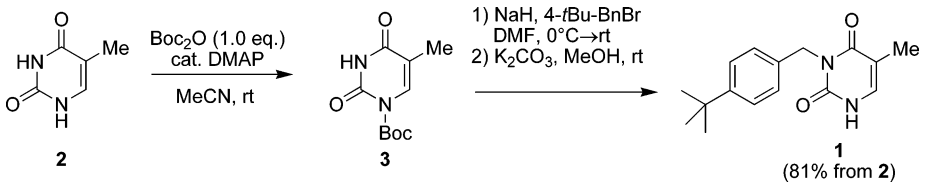
SCHEME 2. Strategy for the *N*-Arylation and *N*-Alkenylation of Nucleobases



SCHEME 3. Synthesis of N^3-(4-*tert*-Butylbenzyl)-Protected Thymine 1



SCHEME 4. Synthesis of N^3-Boc-Protected Thymine 4

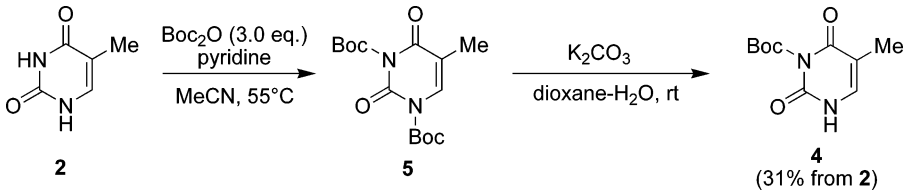
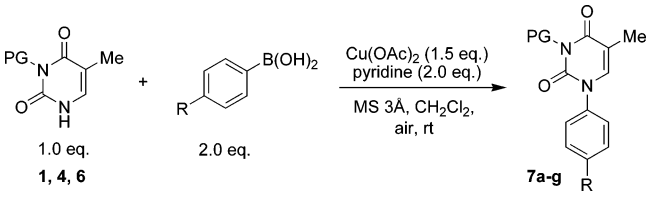


TABLE 1. Influence of N^3 Protection Group on *N*-Arylation of Thymine



entry	R	protection group (PG)	thymine derivative	*N*-aryl product	yield (%)
1	H	4-*t*Bu-Bn	**1**	**7a**	57
2	H	Boc	**4**	**7b**	87
3	H	Bz	**6**	**7c**	92
4	Me	4-*t*Bu-Bn	**1**	**7d**	55
5	Me	Bz	**6**	**7e**	87
6	OMe	4-*t*Bu-Bn	**1**	**7f**	31
7	OMe	Bz	**6**	**7g**	66

in common organic solvents, such as CH_2Cl_2, THF, and EtOAc. The N^3-(4-*tert*-butylbenzyl)-protected thymine **1** was readily obtained in three steps from thymine **2** via the known N^1-mono-Boc derivative **3** (Scheme 3).[20] The N^3-Boc-protected thymine **4** was obtained by selective removal of the N^1-Boc group from bis-Boc derivative **5** with K_2CO_3 (Scheme 4).

The copper-mediated reactions of **1**, **4**, and the known N^3-benzoyl thymine **6**[21] with arylboronic acids were attempted under standard conditions employing pyridine as the ligand/base and CH_2Cl_2 as the solvent (Table 1). The reactions were generally left for 3 days or until no further progress could be detected by TLC. Notably, the Bz-protection group proved superior compared to Boc or 4-*tert*-butylbenzyl. For example, the yields of products **7a**−**c** improved from a 57% yield with 4-*tert*-butylbenzyl (entry 1) to an excellent 92% yield (entry 3) with Bz, with Boc giving a slightly lower yield (entry 2). Hence, mainly the Bz derivative **6** was chosen for further studies. For any given protection group, the yield decreased in the order H > Me > OMe with respect to the para-substituted arylboronic acid employed, demonstrating the sensitivity of the reaction to the nature of the arylboronic acid.

Gratifyingly, the reactions of **6** with various aryl- and alkenylboronic acids proved to be of wide scope and furnished the desired products **8c**−**j** in up to a 98% yield (Table 2). Various groups and substitution patterns on the aryl ring were tolerated, including electron-rich ortho-substituted arylboronic acids (entry 3). Furthermore, the Bz-protected uracil derivative **9**[21] could also be *N*-arylated and *N*-alkenylated in high yields (entries 11 and 12).

Next, we examined suitable cytosine derivatives for the *N*-arylation reaction. However, the use of the known imino derivative **10** (from the condensation of cytosine with *N*,*N*-dimethylformamide diethyl acetal)[22] was unsuccessful and led only to intractable product mixtures, supposedly because of the incompatibility of the imino functionality with the reaction conditions (Chart 1). On the other hand, the commercially available Bz derivative **11** led to mixtures of mono- and di-arylated products in low yields. Fortunately, 4-alkylthio-substituted pyrimidin-2(1*H*)-ones readily undergo substitution with methanolic ammonia, rendering them useful precursors of cytosine derivatives.[23] In addition, their reaction with aq HCl

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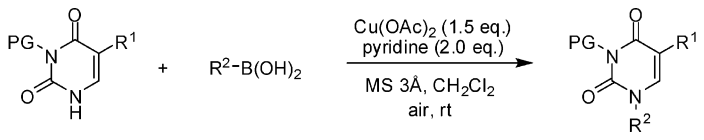
TABLE 2. ***N*-Arylation and *N*-Alkenylation of N^3-Protected Thymine and Uracil**



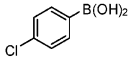
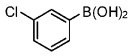
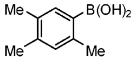
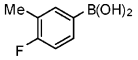
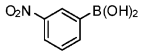
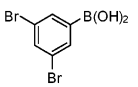
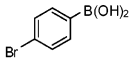
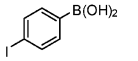
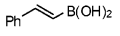
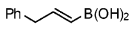
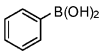
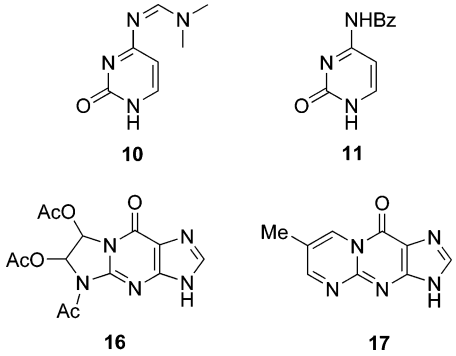
Entry	R^1	Protection group (PG)	R^2-B(OH)$_2$	Thymine/uracil derivative	Product	Yield/%
1	Me	4-*t*Bu-Bn		**1**	**8a**	79
2	Me	Boc		**4**	**8b**	71
3	Me	Bz		**6**	**8c**	67
4	Me	Bz		**6**	**8d**	89
5	Me	Bz		**6**	**8e**	98
6	Me	Bz		**6**	**8f**	75
7	Me	Bz		**6**	**8g**	98
8	Me	Bz		**6**	**8h**	97
9	Me	Bz		**6**	**8i**	97
10	Me	Bz		**6**	**8j**	94
11	H	Bz		**9**	**8k**	88
12	H	Bz		**9**	**8l**	91

CHART 1. Derivatives of Cytosine and Guanine Tested in the *N*-Arylation Reaction



or hydroxides effectively affords the corresponding uracil derivatives.[24] The readily soluble 4-allylthio derivative **12** can be obtained in a high yield (80%) from commercially available 4-thiouracil,[24] and when subjected to the standard reaction conditions, it furnished the desired N^1-arylated and N^1-alkenylated products **13** in good to high yields (Table 3). The reactions proceeded with complete regioselectivity since in no case could the regioisomeric N^3 products be observed.[25]

In our efforts to *N*-arylate and *N*-alkenylate adenine, we were provided, by the work of Garner and Dey on the synthesis of Boc-protected purines, with the bis-Boc-protected adenine **14** which underwent facile *N*-arylation and *N*-alkenylation with different boronic acids (Table 4).[26] Bis-Boc-protected adenine **14** is easily soluble in common organic solvents and obtained in two steps from adenine in an 87% overall yield.[26] By changing the base/ligand to Et_3N and the solvent to DMF, improved yields of the N^9-arylated products could be obtained (compare entries 1−3). In no case could the regioisomeric N^7-aryl or N^7-alkenyl products be detected by ^{1}H NMR analysis of the crude reaction mixture, and the structure of the products was unambiguously confirmed by single-crystal X-ray crystallographic analysis of **15f**.[27] Since the *N*-arylated and *N*-

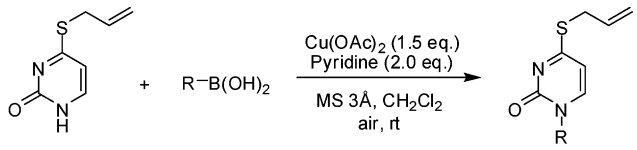
(24) Mizutani, M.; Sanemitsu, Y.; Tamaru, Y.; Yoshida, Z.-I. *Tetrahedron* **1985**, *41*, 5289−5294.

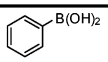
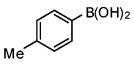
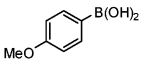
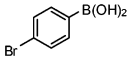
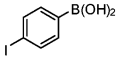
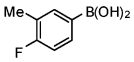
(25) NOE measurements on the products of **13** confirmed that exclusively N^1-arylation and N^1-alkenylation had taken place.

(26) Dey, S.; Garner, P. *J. Org. Chem.* **2000**, *65*, 7697−7699.

(27) See Supporting Information.

TABLE 3. ***N*-Arylation and *N*-Alkenylation of Cytosine/Uracil Precursor 12**

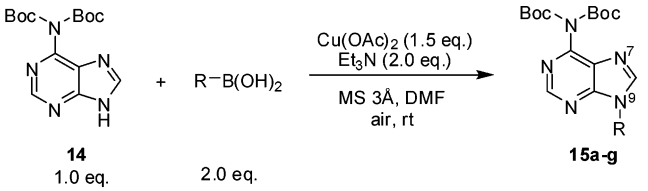


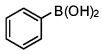
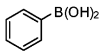
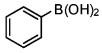
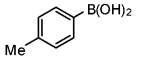
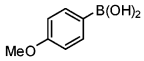
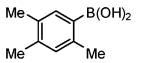
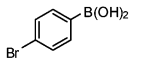
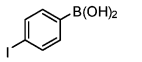
Entry	R-B(OH)$_2$	Product	Yield/%
1		**13a**	78
2		**13b**	87
3		**13c**	62
4		**13d**	91
5		**13e**	85
6		**13f**	93
7		**13g**	83

alkenylated purines can, themselves, serve as ligands for Cu(II),[28] we speculated that the failure to remove any copper salts prior to purification of the products by flash chromatography may render the products less mobile by complexation to Cu(II) species and could potentially lower the yields. Hence, a treatment with an aqueous solution of the strongly Cu(II)-chelating agent EDTA was included in the workup of the reaction mixtures.

The modification of guanine is, in itself, a major challenge because of its insolubility in almost all solvents and its polyfunctional nature with imidazole, amide, and guanidine substructures. Johansson and co-workers have developed several guanine precursors for the N^7- and N^9-alkylation of the imidazole substructure, for example, **16** and **17** (Chart 1) which, subsequent to alkylation, can be converted to the unmasked guanine derivatives following treatment with methanolic KOH.[29] Unfortunately, these protected guanine derivatives proved unstable to the reaction conditions. We, therefore, turned our attention to the bis-Boc-purine **18** reported by Garner and Dey, which can be obtained in two simple steps from 2-amino-6-chloropurine in an 84% overall yield.[26] We envisaged that the products from **18** may be converted directly to the corresponding guanine derivatives. Subjection of **18** to the standard reaction conditions with various boronic acids furnished the desired products **19** in fair to good yields (Table 5). As in the case of **14**, the use of

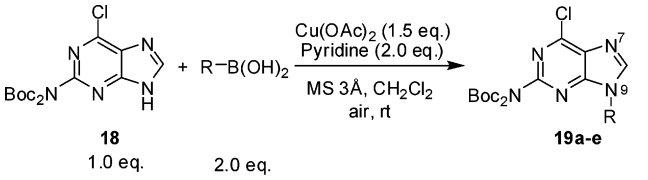
TABLE 4. ***N*-Arylation and *N*-Alkenylation of Bis-Boc-adenine 14**

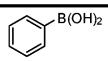
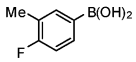
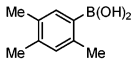
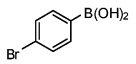
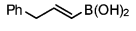


Entry	R-B(OH)$_2$	Product	Yield/%
1[a]		**15a**	57
2[b]		**15a**	64
3		**15a**	93
4		**15b**	69
5		**15c**	77
6		**15d**	47
7		**15e**	86
8		**15f**	77
9		**15g**	85

[a] CH_2Cl_2 was used as the solvent. [b] Pyridine (2.0 equiv) was used as the base/ligand, and CH_2Cl_2 was used as the solvent.

TABLE 5. ***N*-Arylation and *N*-Alkenylation of Guanine Precursor 18**



Entry	R-B(OH)$_2$	Product	Yield/%
1		**19a**	81
2		**19b**	59
3		**19c**	40
4[a]		**19d**	69
5[a]		**19e**	74

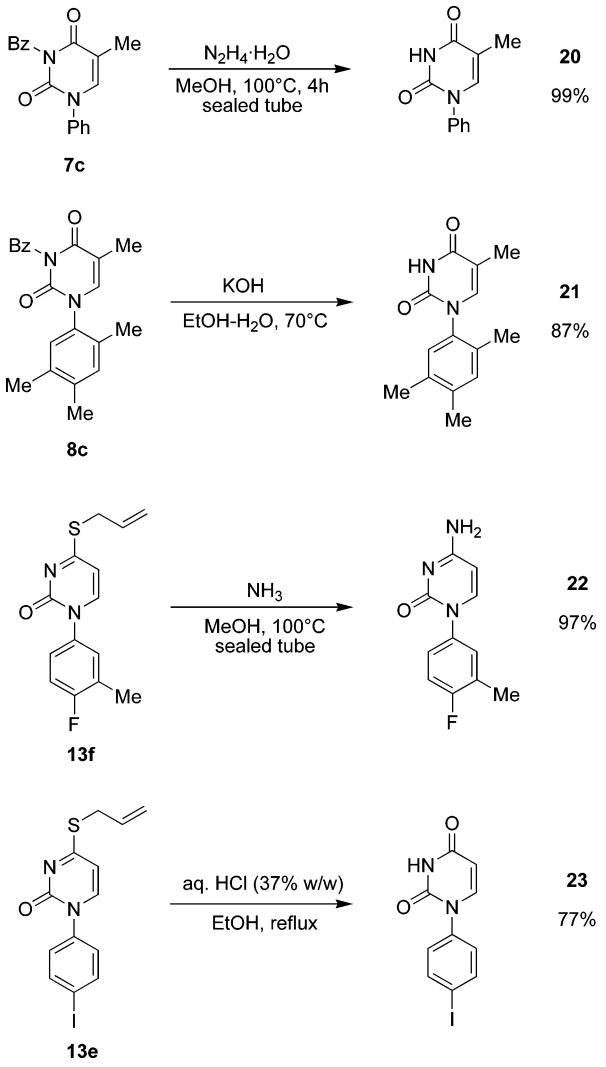
[a] Et_3N was used as the base/ligand, and DMF was used as the solvent.

Et_3N and DMF instead of pyridine and CH_2Cl_2 enhanced the yield of products in some cases (entries 4 and 5). The structure of the N^9-arylated and N^9-alkenylated product was unambiguously confirmed by single-crystal X-ray crystallographic analysis of **19b**.[27]

(28) For some examples, see: (a) Garcia-Teran, J. P.; Castillo, O.; Luque, A.; Garcia-Couceiro, U.; Roman, P.; Lloret, F. *Inorg. Chem.* **2004**, *43*, 5761−5770. (b) Song, B.; Zhao, J.; Griesser, R.; Meiser, C.; Sigel, H.; Lippert, B. *Chem. Eur. J.* **1999**, *5*, 2374−2387. (c) Steinkopf, S.; Liu, Q.; Froeystein, N. A.; Sletten, E. *Acta Chem. Scand.* **1992**, *46*, 446−450. (d) Jitsukawa, K.; Mizutani, M.; Arii, H.; Kubo, I.; Izu, Y.; Ozawa, T.; Masuda, H. *Chem. Lett.* **2004**, *33*, 1302−1303.

(29) (a) Kjellberg, J.; Hagberg, C.-E.; Malm, A.; Noren, J. O.; Johansson, N. G. *Acta Chem. Scand.* **1986**, *B40*, 310−312. (b) Kobe, J.; Kjellberg, J.; Johansson, N. G. *Acta Chem. Scand.* **1987**, *B41*, 564−568.

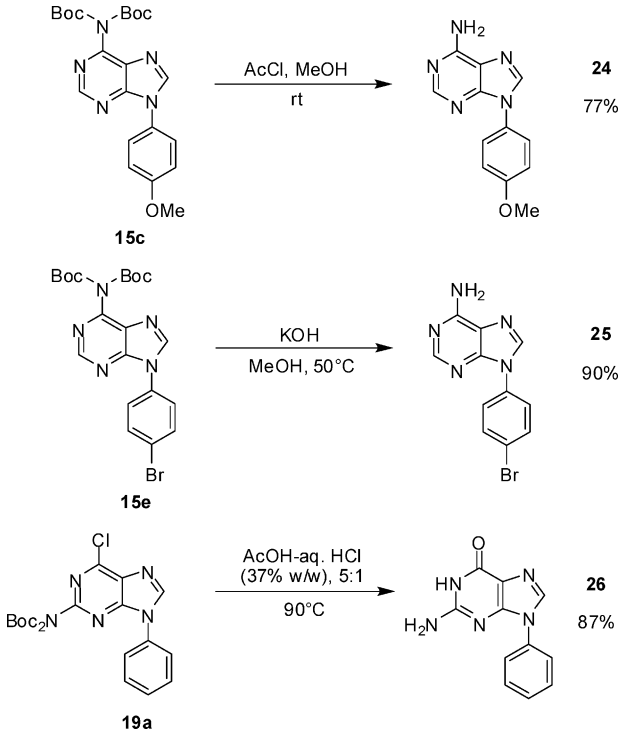
SCHEME 5. Conversion of 7c, 8c, and 13f,e to *N*-Arylated Nucleobases 20−23



The conversion of the protected or masked *N*-arylated pyrimidines **7c**, **8c**, **13f**, and **13e** to the free *N*-arylated nucleobases **20**−**23** was efficiently accomplished as outlined in Scheme 5. The products **7c** and **8c** from protected thymine **6** could be deprotected using either hydrazine hydrate[30] or KOH, while the masked cytosine/uracil derivatives **13f**,**e** were transformed into *N*-arylated cytosine **22** and *N*-arylated uracil **23**, employing NH_3-saturated MeOH and aq HCl, respectively.

The deprotection of the bis-Boc-protected adenine products **15** was unsuccessful by even prolonged exposure to conventional TFA−CH_2Cl_2 solution. Fortunately, the bis-Boc-protected adenine derivatives **15c**,**e** were readily converted to the free *N*-arylated nucleobases **24** and **25** using either treatment with HCl or treatment with KOH, respectively (Scheme 6). The simultaneous removal of the bis-Boc protection and conversion of the chloropurine substructure in **19a** to N^9-phenylguanine **26**[31] was facilitated by treatment with an aq HCl−AcOH mixture. Notably, **26** is an excellent irreversible inhibitor of both guanine deaminase[32] and xanthine oxidase.[33]

SCHEME 6. Conversion of 15c,e and 19a to *N*-Arylated Nucleobases 24−26



Conclusions

Protected or masked derivatives of the five nucleobases, thymine, uracil, cytosine, adenine, and guanine, have been examined for their ability to undergo copper-mediated *N*-arylation and *N*-alkenylation with various boronic acids (Chan−Lam−Evans-modified Ullmann condensation). The reactions tolerated various substitution patterns on the arylboronic acids including ortho-substitution and electron-donating groups. The products were obtained in good to high yields and could subsequently be readily converted to the corresponding deprotected or unmasked *N*-arylated or *N*-alkenylated nucleobases. This constitutes the first general approach to *N*-arylated or *N*-alkenylated derivatives of all five DNA/RNA nucleobases. Further work will focus on the implementation of a protocol catalytic in a copper reagent and on the synthesis of suitable *N*-arylated or *N*-alkenylated nucleobases, including dimers and trimers of nucleobases linked via rigid aryl or alkenyl moieties, for the study of their interaction with DNA and of their behavior on surfaces.

Experimental Section

Typical Procedure for the *N*-Arylation and *N*-Alkenylation of Nucleobases: 3-Benzoyl-1-(4-iodophenyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (8h). To a stirred suspension of dry $Cu(OAc)_2$ (109 mg, 0.60 mmol), N^3-benzoylthymine **6** (92.1 mg, 0.40 mmol), *p*-iodobenzeneboronic acid (198 mg, 0.80 mmol), and activated 3 Å molecular sieves (200 mg) in dry CH_2Cl_2 (3.0 mL) was added pyridine (65 μL, 0.80 mmol) at rt. The mixture was stirred vigorously for 74 h at rt in the presence of air. The reaction mixture was diluted with CH_2Cl_2 (15 mL), filtered through a pad of Celite, and washed with water (15 mL) in the presence of EDTA (200 mg). The colorless organic phase was dried over $MgSO_4$ and was evaporated to dryness in vacuo. The residue was subjected to

(30) (a) Boger, D. L.; Machiya, K. *J. Am. Chem. Soc.* **1992**, *114*, 10056−10058. (b) Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T. *J. Am. Chem. Soc.* **1997**, *119*, 311−325.
(31) Baker, B. R.; Wood, W. F. *J. Med. Chem.* **1967**, *10*, 1101−1105.
(32) Baker, B. R.; Santi, D. V. *J. Med. Chem.* **1967**, *10*, 62−64.
(33) Baker, B. R.; Kozma, J. *J. Med. Chem.* **1967**, *10*, 682−685.

flash chromatography (40:1 CH_2Cl_2−EtOAc) to afford **8h** (168 mg, 97%) as a white solid: $R_f = 0.71$ (10:1 CH_2Cl_2−EtOAc); mp 246−247 °C (from CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (dd, $J = 1.5$, 8.5 Hz, 2H), 7.89 (d, $J = 8.5$ Hz, 2H), 7.88 (s, 1H), 7.79 (tt, $J = 1.5$, 7.5 Hz, 1H), 7.61 (dd, $J = 7.5$, 8.5 Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 1.89 (d, $J = 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.5, 163.0, 148.7, 142.0, 138.1, 138.0 (2C), 135.5, 131.1, 130.5 (2C), 129.4 (2C), 129.2 (2C), 109.3, 94.7, 11.8. HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{18}H_{13}IN_2O_3Na$, 454.9869; found, 454.9872.

3-(4-*tert*-Butylbenzyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (1). To a stirred solution of thymine (2.00 g, 15.9 mmol) in MeCN (100 mL) was added DMAP (19 mg, 0.159 mmol) followed by Boc_2O (3.47 g, 15.9 mmol) at rt. The reaction mixture was stirred for 3 h. The solvent was removed by evaporation in vacuo. The crude product **3** was dissolved in DMF (75 mL), and NaH (760 mg, 60% w/w in oil, 19.0 mmol) was cautiously added at 0 °C. The mixture was stirred for 30 min at 0 °C, and 4-*tert*-butylbenzylbromide (2.9 mL, 16 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, and it was stirred for 30 min. The mixture was diluted with water and was extracted several times with EtOAc. The combined extracts were dried over $MgSO_4$ and were evaporated to dryness in vacuo. The crude product was dissolved in MeOH (30 mL), and powdered K_2CO_3 (1.11 g, 8.00 mmol) was added. The mixture was stirred for 24 h at rt. The mixture was evaporated to dryness, and the residue was extracted several times with CH_2Cl_2. The combined extracts were filtered and were evaporated to dryness in vacuo to leave the pure **1** (3.55 g, 13.0 mmol) as a white solid: mp 197−199 °C (from CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (s, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.21 (d, $J = 8.2$ Hz, 2H), 4.93 (s, 2H), 1.79 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.8, 151.5, 149.4, 136.7, 134.5, 127.5 (2C), 125.0 (2C), 107.2, 42.5, 34.1, 31.1, 12.5 (3C). HRMS (ES) *m*/*z*: MH^+ calcd for $C_{16}H_{21}N_2O_2$, 273.1603; found, 273.1610.

Di-*tert*-butyl-5-methyl-2,4-dioxopyrimidine-1,3(2*H*,4*H*)-dicarboxylate (5). Thymine **2** (5.0 g, 22.1 mmol), di-*tert*-butyl dicarbonate (13.0 g, 65 mmol), pyridine (8 mL), and MeCN (40 mL) were stirred together for 4 h at 55 °C. The reaction mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed by evaporation in vacuo. The residue was purified by flash chromatography (CH_2Cl_2) affording **5** (6.5 g, 90%) as a white solid: mp 147−148 °C (from CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 1.94 (s, 3H), 1.58 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 148.5, 147.7, 145.9, 134.8, 111.9, 87.5, 87.2, 28.0, 27.6, 12.8 (3C), 12.8 (3C). HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{15}H_{22}N_2O_6Na$, 349.1376; found, 349.1380.

***tert*-Butyl-5-methyl-2,6-dioxo-2,3-dihydropyrimidine-1(6*H*)-carboxylate (4).** Compound **5** (6.0 g, 18.4 mmol) was dissolved in dioxane (20 mL), and a solution of K_2CO_3 (3.8 g, 27.6 mmol) in water (10 mL) was slowly added. After 40 min, the reaction was quenched by the addition of glacial acetic acid (10 mL). The reaction mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ and filtered, and the solvents were removed by evaporation in vacuo. The residue was subjected to flash chromatography (9:1 CH_2Cl_2−EtOAc) yielding **4** (1.4 g, 34%) as a white solid: $R_f = 0.2$ (9:1 CH_2Cl_2−EtOAc); mp 310−312 °C (from CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (br s, 1H), 7.06 (s, 1H), 1.92 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 151.0, 148.1, 136.1, 110.8, 87.2, 27.7, 12.5 (3C). HRMS (ES) *m*/*z*: $[M + Na]^+$ calcd for $C_{10}H_{14}N_2O_4Na$, 249.0851; found, 249.0841.

5-Methyl-1-phenylpyrimidine-2,4(1*H*,3*H*)-dione (20).[12] To a stirred solution of **7c** (27.6 mg, 0.090 mmol) in MeOH (2.0 mL) was added hydrazine hydrate (58 μL, 1.20 mmol). The clear solution was heated at 100 °C in a sealed tube for 4 h. The mixture was cooled and was evaporated to dryness in vacuo. The residue was subjected to flash chromatography (1:1 CH_2Cl_2−EtOAc) to afford **20** (18 mg, 99%) as a white solid: $R_f = 0.51$ (1:1 CH_2Cl_2−EtOAc); mp 199−200 °C (lit. mp 198−200 °C;[12] from CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (br s, 1H), 7.46−7.51 (m, 2H), 7.40−7.44 (m, 1H), 7.34−7.36 (m, 2H), 7.19 (q, $J = 1.5$ Hz, 1H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 150.3, 140.8, 138.6, 129.6 (2C), 128.8, 126.4 (2C), 111.2, 12.4. HRMS (ES) *m*/*z*: MH^+ calcd for $C_{11}H_{11}N_2O_2$, 203.0821; found, 203.0820.

5-Methyl-1-(2,4,5-trimethylphenyl)pyrimidine-2,4(1*H*,3*H*)-dione (21). To a stirred solution of **8c** (52.3 mg, 0.15 mmol) in EtOH−H_2O (3.0 mL, 2:1 v/v) was added KOH (84 mg, 1.50 mmol), and the mixture was heated at 70 °C for 4 h. The mixture was cooled and was extracted twice with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and were evaporated to dryness in vacuo. The residue was subjected to flash chromatography (1:1 CH_2Cl_2−EtOAc) to afford **21** (31.8 mg, 87%) as a white solid: $R_f = 0.68$ (1:1 CH_2Cl_2−EtOAc); mp 204−205 °C (from CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.08 (s, 1H), 7.00 (q, $J = 1.0$ Hz, 1H), 6.96 (s, 1H), 2.25 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 1.95 (d, $J = 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 150.2, 141.3, 138.3, 135.9, 135.0, 132.5, 132.5, 128.2, 110.6, 19.5, 19.3, 17.0, 12.4. HRMS (ES) *m*/*z*: MH^+ calcd for $C_{14}H_{17}N_2O_2$, 245.1290; found, 245.1285.

4-Amino-1-(4-fluoro-3-methylphenyl)pyrimidin-2(1*H*)-one (22). Compound **13f** was dissolved in MeOH (5.0 mL), and the solution was saturated with NH_3 by bubbling NH_3 gas through it at rt. The solution was heated in a sealed tube at 100 °C for 19 h. The resulting white suspension was cooled, and Et_2O (15 mL) was added. The mixture was further cooled in an ice bath and filtered. The white solid was washed several times with Et_2O and was dried in vacuo to afford pure **22** (63.7 mg, 97%) as a white solid: mp > 250 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, $J = 7.50$ Hz, 1H), 7.27−7.32 (m, 3H), 7.18−7.20 (m, 2H), 5.78 (d, $J = 7.5$ Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 159.2, 155.0, 145.8, 137.3, 129.8 (d, $J = 5.3$ Hz), 126.0 (d, $J = 8.4$ Hz), 124.7 (d, $J = 18.3$ Hz), 115.1 (d, $J = 23.6$ Hz), 94.1, 14.1. HRMS (ES) *m*/*z*: MH^+ calcd for $C_{11}H_{11}FN_3O$, 220.0886; found, 220.0890.

1-(4-Iodophenyl)pyrimidine-2,4(1*H*,3*H*)-dione (23). Compound **13e** (100 mg, 0.27 mmol) was dissolved in a mixture of aq HCl (1 mL, 37% w/w) and EtOH (2 mL) and was refluxed for 3 h. The reaction mixture was cooled to rt and was partitioned between CH_2Cl_2 (25 mL) and water (10 mL). The organic layer was separated, and the aqueous phase was extracted twice with CH_2Cl_2 (25 mL). The combined extracts were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was washed with Et_2O (10 mL) and was filtered, yielding **23** (67 mg, 79%) as a white solid: mp 291−292 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.4 (br s, 1H), 7.82 (d, $J = 9.0$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.22 (d, $J = 9.0$ Hz, 2H), 5.66 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.3, 150.9, 145.8, 139.3, 138.6 (2C), 129.8 (2C), 102.5, 95.0. HRMS (ES) *m*/*z*: MH^+ calcd for $C_{10}H_8IN_2O_2$, 314.9630; found, 314.9639.

9-(4-Methoxyphenyl)-9*H*-purin-6-amine (24).[34] To a stirred solution of **15c** (57.3 mg, 0.13 mmol) in MeOH (3.0 mL) was added carefully AcCl (185 μL, 2.6 mmol) at rt. The mixture was stirred for 72 h, and the white precipitate was filtered from the solution, washed several times with Et_2O, and dried in vacuo to afford pure **24** (24.2 mg, 77%) as a white solid: mp > 290 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (br s, 1H), 8.99 (br s, 1H), 8.80 (s, 1H), 8.55 (s, 1H), 7.69 (d, $J = 9.0$ Hz, 2H), 7.16 (d, $J = 9.0$ Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 150.7, 148.2, 145.5, 143.3, 126.5, 125.7 (2C), 118.7, 114.8 (2C), 55.6. HRMS (ES) *m*/*z*: MH^+ calcd for $C_{12}H_{12}N_5O$, 242.1042; found, 242.1047.

(34) Young, R. C.; Jones, M.; Milliner, K. J.; Rana, K. K.; Ward, J. G. *J. Med. Chem.* **1990**, *33*, 2073−2080.

9-(4-Bromophenyl)-9*H*-purin-6-amine (25).[19] To a stirred solution of **15e** (123 mg, 0.25 mmol) in MeOH (2.5 mL) was added KOH (140 mg, 2.50 mmol). The mixture was heated at 50 °C for 19 h. The white suspension was cooled and filtered. The white precipitate was washed with MeOH and Et_2O and dried in vacuo to afford pure **25** (65.4 mg, 90%) as a white solid: mp > 280 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.22 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.79 (d, J = 9.0 Hz, 2H), 7.44 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.4, 153.3, 149.0, 139.4, 134.5, 132.4 (2C), 124.7 (2C), 120.0, 119.3. HRMS (ES) m/z: MH^+ calcd for $C_{11}H_9{}^{79}BrN_5$, 290.0041; found, 290.0050.

2-Amino-9-phenyl-1*H*-purin-6(9*H*)-one (26).[31] To a stirred suspension of **19a** (89.2 mg, 0.20 mmol) in AcOH (3.0 mL) was added carefully aq HCl (0.6 mL, 37% w/w), and the mixture was heated at 90 °C for 17 h. The solution was cooled and was co-evaporated twice with toluene (~15 mL) to dryness in vacuo. The crude product was dissolved in minimum MeOH and was evaporated with silica gel (~0.5 g) to dryness. The resulting powder was subjected to flash chromatography (EtOAc → 200:40:1 EtOAc−MeOH−Et_3N → 10:10:1 EtOAc−MeOH−Et_3N) to yield **26** (39.5 mg, 87%) as a white powder: R_f = 0.19 (200:40:1 EtOAc−MeOH−Et_3N); mp > 300 °C (decomp); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.79 (br s, 1H), 8.05 (s, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 6.61 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 153.9, 150.9, 136.4, 135.1, 129.3 (2C), 127.5, 123.7 (2C), 117.2; HRMS (ES) m/z: MH^+ calcd for $C_{11}H_{10}N_5O$, 228.0885; found, 228.0892.

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Supporting Information Available: General experimental methods, full characterization of compounds, ORTEP presentations of **15f** and **19b**, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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