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Switching the Regioselectivity of Direct C–H Arylation of 1,3-Dimethyluracil

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An interesting dichotomy in the regioselectivity and mechanism of direct C–H arylation of 1,3-dimethyluracil was observed. Its Pd-catalyzed reactions with diverse aryl halides in the absence of CuI lead preferentially to 5-aryluracils, while reactions in the presence of CuI give 6-aryl derivatives as the major products. Cu-mediated reactions (in the absence of a Pd catalyst) proceed with lower efficiency but give exclusively 6-aryluracil derivatives.

Introduction

Uracil bases and nucleosides bearing aryl groups in positions 5 or 6 are an important class of compounds displaying diverse biological activities[1] (cytostatic, antiviral, antagonists of GnRH, etc.). In addition, arylation in position 5 is often used for labeling of nucleotides, oligonucleotides, and DNA for applications in bioanalysis or chemical biology.[2] The 5- or 6-aryluracils can be prepared by heterocyclization[3] or by cross-coupling reactions[4] of halouracils with arylboronic acids or -stannanes or of metalated uracils with aryl halides. However, some aryluracils are still difficult to prepare and, therefore, development of alternative methodologies is of interest.

Direct C–H arylations have recently emerged as an alternative to cross-couplings. Extensive research has resulted in the development of efficient methodologies for C–H arylation of diverse aromatics and heterocycles.[5–8] Although a number of transition-metal complexes were used as catalysts, Pd complexes are the most versatile catalysts, successful in most cases. The reactions are performed either in the presence or in the absence of Cu^I salts. The Cu-free reactions were proved to proceed by a concerted metalation–deprotonation (CMD) mechanism,[6] which consists of the oxidative addition of the aryl halide to the Pd catalyst and attack of the resulting complex at the arene C–H bond with the assistance of a base to simultaneously cleave the C–H bond and form a C–Pd bond, followed by reductive elimination to afford the biaryl product. On the other hand, in several Cu-mediated reactions, direct metalation of the arene C–H bond by a base and copper salt was observed,[7] which generated an aryl cuprate that then underwent cross-coupling with an aryl halide (either Pd-catalyzed or noncatalyzed Ullmann type coupling). While electron-rich heterocycles are usually excellent substrates for C–H arylation, electron-poor heterocycles (i.e. pyridines or pyrimidines) have a lower reactivity, and their corresponding *N*-oxides are used instead for the C–H arylations.[8] Apart from Cu-mediated Pd-catalyzed reactions, Pd-free arylations are also reported[9] in the presence of excess Cu salts, but usually such reactions are less efficient.

Recently, we have developed Pd-catalyzed C–H arylations of purine bases and nucleosides to position 8 in the presence of CuI and Cs_2CO_3[10] and Ir-catalyzed C–H borylations of 7-deazapurines.[11] In order to extend the use of C–H arylations in nucleoside/nucleic acid chemistry, we have tried to develop the C–H arylation of 1,3-dimethyluracil as a model compound for uracil bases and nucleosides. So far, only one example of an intramolecular C–H arylation of related compounds that leads to fused heterocycles has been reported,[12] during the course of our study.

Results and Discussion

1,3-Dimethyluracil (**1**) was selected as a model compound for pyrimidine nucleobases and nucleosides. It contains two C–H bonds capable of arylation – positions 5 and 6. Position 5 is known to be the preferred site for electrophilic substitution,[3] while C–H in position 6 is more acidic and undergoes metalation.[4] The direct C–H arylation of **1** was optimized with the reaction with *p*-tolyl iodide (**2a**) by using $Pd(OAc)_2$ in combination with diverse ligands and with varying amounts of CuI in the presence of Cs_2CO_3 (Scheme 1, Table 1). The ligand-free conditions, in analogy to the arylation of purines[10] at 160 °C (Entry 1), gave moderate conversion to a mixture of 5-tolyl (**3a**) and 6-tolyl (**4a**) derivatives in a 1:4 ratio. The regioisomers were separable only by repeated flash chromatography and were assigned by HMBC NMR spectroscopy (see Supporting Infor-

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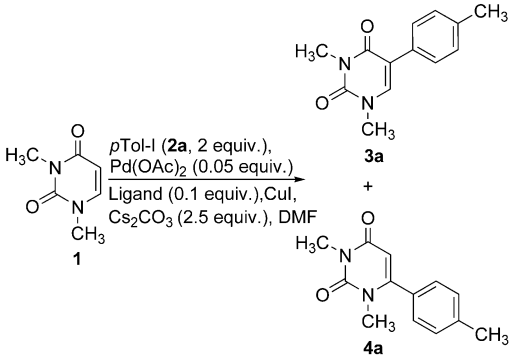
mation). When using the PPh_3 ligand at 140 °C, the yield was lower and the ratio **3a**/**4a** was 1:19 (Entry 2). The use of $(t\text{Bu})_2\text{PMe}$[13] in the absence of CuI at 130 °C gave quantitative conversion to an almost equimolar mixture **3a**/**4a**.



Scheme 1. C–H arylation of **1** with Tol-I.

Table 1. Optimization of conditions of C–H arylation of **1**.

Entry	Ligand	CuI [equiv.]	*T* [°C]	Conversion [%]	Ratio **3a**/**4a**
1	–	3	160	53	20:80
2	PPh_3	3	140	31	5:95
3	$(t\text{Bu})_2\text{PMe}\cdot\text{HBF}_4$[a]	–	130	99	55:45
4	$(t\text{Bu})_2\text{PMe}\cdot\text{HBF}_4$[a]	1	130	56	31:69
5	$(t\text{Bu})_2\text{PMe}\cdot\text{HBF}_4$	3	160	62	19:81
6	$P(t\text{Bu})_3\cdot\text{HBF}_4$[a]	–	130	57	62:38
7	$P(t\text{Bu})_3\cdot\text{HBF}_4$[a]	3	130	72	14:86
8	$P(o\text{Tol})_3$	3	160	68	22:78
9	$P(p\text{-FPh})_3$	3	160	53	9:91
10	$P(\text{perFPh})_3$	–	160	62	86:14
11	$P(\text{perFPh})_3$	0.1	160	62	86:14
12	$P(\text{perFPh})_3$	1	160	50	24:76
13	$P(\text{perFPh})_3$	3	160	78	6:94
14	–[b]	3	160	35	0:100
15	phenanthroline[b,c]	0.2	140	22	4:96

[a] $Pd(OAc)_2$ (0.1 equiv.), ligand (0.2 equiv.). [b] In the absence of $Pd(OAc)_2$. [c] K_2CO_3, DMF/*m*-xylene (1:1).

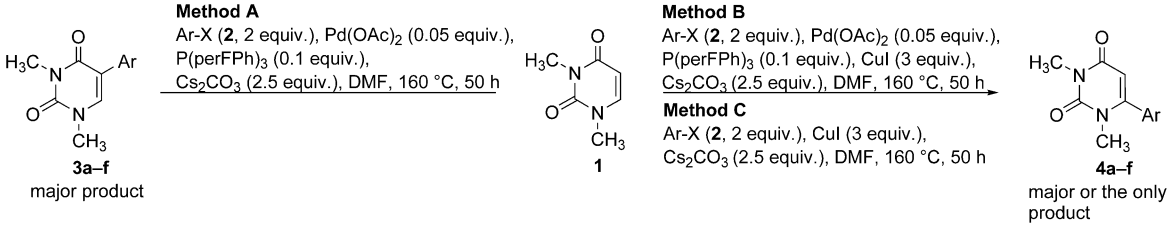
Interestingly, addition of 1 or 3 equiv. CuI dramatically lowered the yield (to 56 and 62%, respectively), but increased the selectivity of **4a** (Entries 3–5). The use of $P(t\text{Bu})_3$ at 130 °C in the absence of CuI gave 57% conversion to a ca.2:1 mixture of **3a**/**4a**, while in the presence of CuI, the ratio was switched to ca. 1:6 (Entries 6 and 7). A similar result was obtained when using $P(o\text{-Tol})_3$ or $P(p\text{-FPh})_3$[14] in the presence of CuI (ratio 1:4 or 1:10, Entries 8 and 9). $P(\text{perFPh})_3$ was then used as a ligand in a series of experiments with varying amounts of CuI (Entries 10–13). Reactions in the absence or with 0.1 equiv. CuI gave a decent (62%) conversion to a ca. 6:1 mixture of **3a**/**4a**, while in the presence of 1 or 3 equiv. CuI, the reaction afforded **4a** as the major product (ratios 1:3 and 1:16, respectively). When the reaction was performed in the presence of 3 equiv. CuI and in the absence of any Pd catalyst and ligand (Entry 14), the conversion was lower but the reaction was fully regioselective to give only the product of C6-arylation (**4a**). The last optimization experiment involved the use of CuI in the presence of phenanthroline as ligand (in analogy to recent Cu-mediated C–H arylation of caffeine[9b]), but these conditions gave a low conversion (Entry 15).

Three different procedures were further utilized in preparative experiments with diverse aryl halides: (A) $Pd(OAc)_2$ in combination with $P(\text{perFPh})_3$ in the absence of CuI, (B) the same reagents but in the presence of 3 equiv. CuI, and (C) CuI in the absence of Pd catalyst and ligand (Scheme 2, Table 2). The reactions with *p*Tol-I (**2a**), *o*-Tol-I (**2b**), 4-MeOPh-I (**2c**), and Ph-I (**2d**) under conditions A gave 5-aryluracils **3a**–**d** as the major products in 54–80% yields (Entries 1, 4, 7, and 10), while under conditions B, the selectivity was reversed to afford 6-aryl derivatives **4a**–**d** as the major products in 54–72% yields (Entries 2, 5, 8, and 11). In all cases, minor amounts of the other regioisomer were isolated. Conditions C generally gave lower conversions but a high regioselectivity to give 6-substituted uracils **4a**–**d** as the only products (35–59% yields). Two aryl bromides (**2e**,**f**) were also successfully used for the C–H arylation of **1** under the same conditions (Entries 13–18) to show similar conversions and selectivity (with the exception of the reaction of **2e** under conditions B, which gave **4e** as the only product). Electron-poor aryl iodides (1-iodo-4-nitrobenzene, 4-iodobenzonitrile, 3-iodopyridine, 5-iodouracil, 5-iodo-1,3-dimethyluracil) were also tried in these reactions under conditions A–C, but in all cases, no reactions (or very low conversions <10%) were observed. Apparently this methodology is only applicable to electron-rich and neutral aryl halides. No product of 5,6-diarylation was observed in any of those reactions, and also additional experiments of further arylation of 5-aryluracil **3a** under conditions B and arylation of 6-aryluracil **4a** under conditions A with another aryl iodide (**2c**) did not proceed. The second C–H arylation probably does not proceed because of steric reasons.

The dichotomy of the reaction regioselectivity clearly indicates different reaction mechanisms in each case. While the reactions in the absence of CuI presumably proceed through the CMD mechanism[6] and thus follow the regioselectivity of electrophilic substitution (position 5), the reactions in the presence of CuI most likely proceed through cupration[7] of the heterocycle in the position of the more acidic H (position 6). The reaction in the absence of a Pd catalyst, which proceeds through an Ullmann coupling, is less efficient (but more selective) than reactions in the presence of $Pd(OAc)_2$ and ligand. This shows that Pd catalysis does occur even in the presence of CuI and increases the efficiency of those reactions.

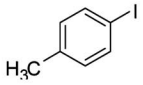
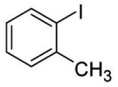
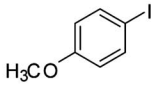
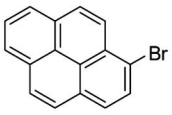
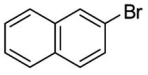
Conclusions

Pd-catalyzed and/or Cu-mediated direct C–H arylations of 1,3-dimethyluracil with diverse electron-rich aryl halides were developed. Reactions in the absence of CuI provide 5-aryluracils **3** as the major products, while the reactions in the presence of CuI preferentially give 6-aryluracils **4**. Fur-



Scheme 2. Preparative C–H arylations of **1**.

Table 2. C–H arylations of **1** with diverse aryl halides.

Entry	Ar-X		Method	Conversion [%]	Ratio **3**/**4** [%]	Yield of **3** [%]	Yield of **4** [%]
1		**2a**	A	62	86:14	54	7
2			B	78	6:94	5	72
3			C	35	0:100	0	35
4		**2b**	A	96	82:18	80	15
5			B	60	7:93	5	54
6			C	48	0:100	0	48
7		**2c**	A	68	81:19	56	12
8			B	68	9:91	6	62
9			C	59	0:100	0	59
10		**2d**	A	76	88:12	68	8
11			B	68	12:88	8	60
12			C	37	0:100	0	37
13		**2e**	A	88	77:23	68	20
14			B	68	0:100	0	68
15			C	36	0:100	0	36
16		**2f**	A	53	79:21	42	10
17			B	89	10:90	9	80
18			C	24	0:100	0	24

ther developments of the methodology for the synthesis of libraries of substituted uracils and for the synthesis of pyrimidine nucleosides are underway.

Experimental Section

General Procedure for C–H Arylation (Methods A and B): DMF (3 mL) was added through a septum to an argon purged vial containing 1,3-dimethyluracil (**1**, 70 mg, 0.5 mmol), aryl halide (**2a**–**h**, 1 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $P(perFPh)_3$ (26.6 mg, 0.05 mmol), and Cs_2CO_3 (407 mg, 1.25 mmol) in the absence (*Method A*) or in the presence (*Method B*) of CuI (286 mg, 1.5 mmol). The reaction mixture was stirred at 160 °C for 50 h. After cooling to room temperature, the mixture was diluted with chloroform (20 mL), and the solvents were evaporated under reduced pressure. A mixture of C-5 and C-6 substituted products were isolated by column chromatography (hexanes/ethyl acetate, 8:2). A second flash column chromatography (hexanes/THF, 8:2) was used to separate the isomers.

3a: Method A, yield 62 mg (54%), white crystals from $CHCl_3$/*n*-heptane. M.p. 162–163 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, CH_3-*p*), 3.42 (s, 3 H, CH_3, 3-H), 3.47 (s, 3 H, CH_3, 1-H), 7.20 (m, 2 H, *m*-$C_6H_4CH_3$-H), 7.26 (s, 1 H, 6-H), 7.39 (m, 2 H, *o*-$C_6H_4CH_3$-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.17 (CH_3-*p*); 28.23 (CH_3, C-3), 37.06 (CH_3, C-1), 114.41 (C-5), 128.12 (CH-*o*-$C_6H_4CH_3$), 129.14 (CH-*m*-$C_6H_4CH_3$), 129.90 (C-*i*-$C_6H_4CH_3$), 137.73 (C-*p*-$C_6H_4CH_3$), 139.93 (CH, C-6), 151.48 (C-2), 162.41 (C-4) ppm. IR: 2921, 2853, 1688, 1643, 1515, 1448, 1431, 1408, 1350, 1208, 1125. MS (EI): *m*/*z* (%) = 77 (14), 104 (36), 116 (38), 132 (57), 145 (19), 158 (17), 172 (56), 230 (100) [M]. HRMS: calcd. for $C_{13}H_{14}N_2O_2$ [M] 230.1055; found 230.1053. $C_{13}H_{14}N_2O_2$ (230.3): calcd. C 67.81, H 6.13, N 12.17; found C 67.71, H 6.15, N 12.05.

4a: Method B, yield 83 mg (72%). M.p. 105–107 °C. ^{1}H NMR (499.8 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3-*p*), 3.23 (s, 3 H, CH_3, 1-H), 3.41 (s, 3 H, CH_3, 3-H), 5.69 (s, 1 H, 5-H), 7.22 (m, 2 H, *o*-$C_6H_4CH_3$-H), 7.29 (m, 2 H, *m*-$C_6H_4CH_3$-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.35 (CH_3-*p*), 28.00 (CH_3, C-3), 34.57 (CH_3, C-1), 102.36 (CH, C-5), 127.67 (CH-*o*-$C_6H_4CH_3$), 129.59 (CH-*m*-$C_6H_4CH_3$), 130.48 (C-*i*-$C_6H_4CH_3$), 140.46 (C-*p*-$C_6H_4CH_3$), 152.76 (C-2), 154.76 (C-6), 162.51 (C-4) ppm. IR: 2923, 2854, 1702, 1651, 1618, 1514, 1456, 1430, 1390, 1368, 1185, 1007 cm^{-1}. MS (EI): *m*/*z* (%) = 65 (14), 77 (11), 82 (25), 91 (30), 101 (10), 105 (19), 116 (30), 132 (93), 144 (30), 158 (6), 172 (60), 202 (7), 230 (100) [M]. HRMS: calcd. for $C_{13}H_{14}N_2O_2$ [M] 230.1055; found 230.1053.

Supporting Information (see footnote on the first page of this article): Characterization data for all other compounds and copies of NMR spectra are given.

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