ORGANIC LETTERS

2008
Vol. 10, No. 9
1715−1718

Oxidative Amination of Cuprated Pyrimidine and Purine Derivatives

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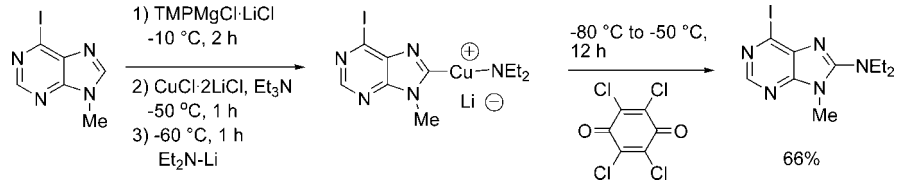
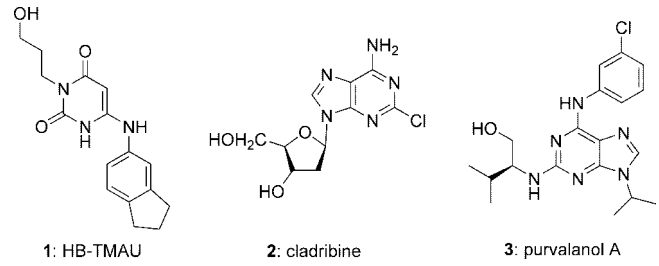
Received February 16, 2008

ABSTRACT



Using regioselective cuprations (via magnesiations), various primary, secondary and tertiary aminated pyrimidine and purine derivatives were prepared by the oxidative coupling of lithium amidocuprates using chloranil. DNA and RNA units such as aminated uracil or thymine, and adenine, as well as a CDK inhibitor, purvalanol A, were all obtained under mild conditions and satisfactory yields.

The structural variations of purine and pyrimidine derivatives might modify their binding with the target protein.[1,2] Especially, aminated purine and uracil are present in drugs such as the antibiotic HB-TMAU (**1**),[3,2b] cladribine (**2**),[4] an anticancer drug, or purvalanol A (**3**),[5] a CDK inhibitor (Figure 1). Organocopper intermediates[6] due to their exceptional functional group tolerance would be ideal reagents for the functionalization of purines and pyrimidines. Recently, we have reported an efficient oxidative amination procedure



1: HB-TMAU **2**: cladribine **3**: purvalanol A

Figure 1. Drugs including aminated uracil or purine cores.

of lithium amidocuprates using chloranil.[7] Herein, we have extended the scope of this method to the amination of purine and pyrimidine cores using new regioselective cuprations (via

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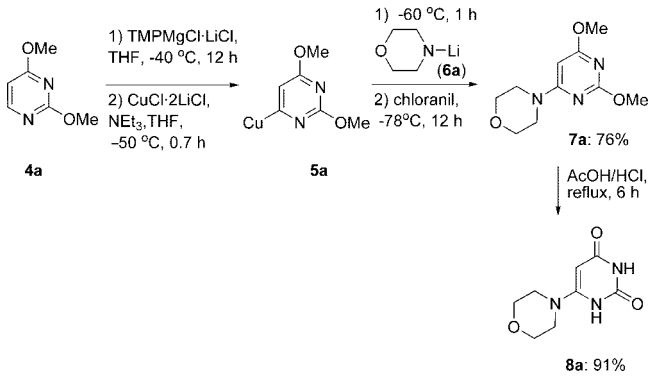
10.1021/ol800353s CCC: $40.75
Published on Web 04/09/2008

Scheme 1. Direct Amination in 6-Position of Uracil



magnesiations) of pyrimidine and purine derivatives. Thus, starting from commercially available 2,4-dimethoxypyrimidine (**4a**, Scheme 1), the addition of TMPMgCl·LiCl[8] (TMP = 2,2,6,6-tetramethylpiperidyl; 1.1 equiv, −40 °C, 12 h) led to an unprecedented direct C6-metalation.[9] The corresponding C6-magnesiated intermediate afforded after transmetalation using CuCl·2LiCl (1.2 equiv, −60 °C) the corresponding copper reagent (**5a**). After the reaction with N-lithium morpholide (**6a**; 2 equiv, −60 °C, 1 h), the corresponding amidocuprate is oxidized using chloranil (1.2 equiv, −78 °C, 12 h) giving the expected aminated product **7a** in 76% yield. A subsequently treatment of **7a** under acidic conditions provided the 6-N-morpholino-uracil (**8a**) in 91% yield (Scheme 1). Similarly, starting from the organocopper reagent **5a**, the addition of LiHMDS (**6b**) or of the lithiated N-TBS aniline derivative **6c**, furnished after oxidation with chloranil, the corresponding products 4-amino-2,6-dimethoxypyrimidine (**7b**, 81%, obtained after desilylation using TBAF, THF, 25 °C, 0.3 h, entry 1 of Table 1) and **7c**, a precursor of HB-TMAU (**1**); (76%, entry 2).[10] Interestingly, the direct C6-magnesiation and cupration of 5-methyl-2,4-dimethoxypyrimidine (**4b**, entry 3) using successively TMPMgCl·LiCl (1.1 equiv, −5 °C, 3 h) and CuCl·2LiCl provided the cuprated protected thymine **5b**. An oxidative amination of **5b** with the sterically hindered amides N-lithium morpholide or TMPLi (**6a–d**) provided the 6-N-morpholino-thymine **8b** (69%, after acidic deprotection, entry 3) and the aminated 5- methyl-2,4-dimethoxypyrimidine **7d** (70%, entry 4).

The conventional amination of protected uracil in position 5 often first involves a nitration[10] or harsh reaction conditions for the substitution.[11] Using our method, starting from readily available 5-bromo-2,4-dimethoxypyrimidine (**4c**), a Br/Mg exchange with *i*-PrMgCl·LiCl[12] followed by a transmetalation with CuCl·2LiCl led after reaction with LiHMDS (**6b**) or the lithiated N-TBS 3,4,5-trimethoxyaniline (**6e**) to the 5-aminated uracil derivative **7e** and **7f** (68–79%, entries 5–6). Commercially available 6-chloro-2,4-dimethoxypyrimidine (**4d**) was metalated at C5 position (TMPMgCl·LiCl, 25 °C, 1 h; then CuCl·2LiCl) affording the corresponding organocopper reagent **5d** (entries 7–8). The reaction with the N-lithium amides **6a-f** provided the corresponding 6-chloro-5-amino-2,4-dimethoxypyrimidine derivatives **7g–h** (78%). Polyhalogenated pyrimidines **4e–f** were regioselectively magnesiated, [8] cuprated (**5e–f**) and oxidatively aminated by the secondary lithium amides **6a–f** leading to the aminated pyrimidines (**7i–j**, 66–70%, entries 9–10).

The conventional amination of purines in positions-2, –6 and –8[13] involves high temperature for the substitution,[14] or Pd-catalyzed amination from halogenated purines.[15] However, the chloranil-mediated oxidation proceeds under much milder conditions. We have concentrated our efforts on the amination of these positions. Thus, a selective magnesiation in position-8 could be achieved by the reaction of the purines **4g** and **4h** with TMPMgCl·LiCl under convenient reaction conditions (THF, −10 °C, 2–3 h) giving after transmetalation the 8-cuprated purines **5g–h** which by oxidative amination with N-lithium morpholide (**6a**) or Et_2NLi (**6g**) provided the expected 8-aminated purines **7k–l** (63–66%, entries 11–12). Using *Dvořák*'s conditions[16] for the selective magnesiation in position 2 on the iodopurine **4i** and a copper-(I) transmetalation, the reaction of the lithium amide **6a** to the corresponding organocopper reagent **5i** followed by the treatment with chloranil (−78 °C, 2 h), gave the desired 2-aminopurine **7m** in 69% yield (entry 13). The mild amination conditions allowed also an alternative method to the nucleophilic substitution for the amination at C6 position.[17] Thus, the 6-iodopurine nucleoside **4j**[18] was successively magnesiated, cuprated and finally aminated with **6f** furnishing the adenosine derivative **7n** (70%, entry 14). Via a chemoselective I/Mg exchange reaction using *i*-PrMgCl·LiCl on the 9-alkylated 2-chloro-6-iodopurine **4k**

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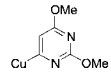
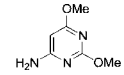
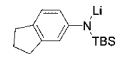
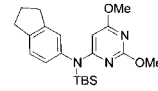
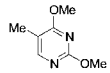
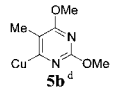
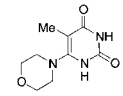
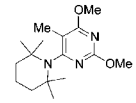
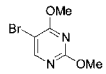
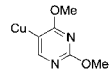
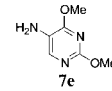
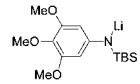
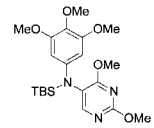
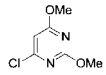
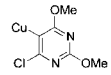
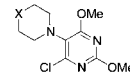
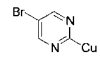
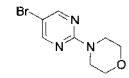
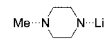
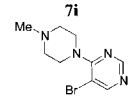
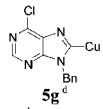
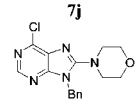
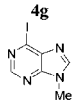
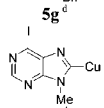
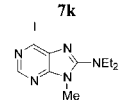
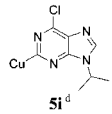
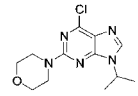
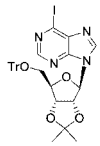
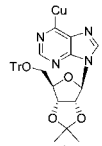
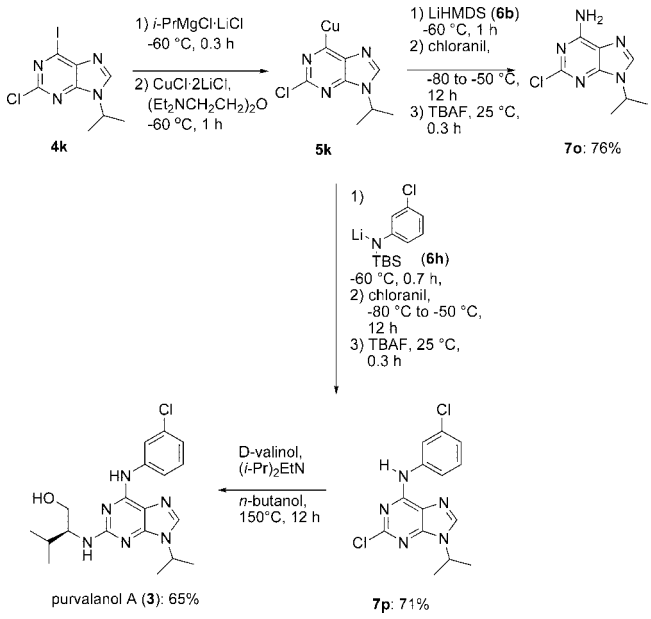
Table 1. Amination of Cuprated Pyrimidines and Purines Derivatives of Type **5**

Entry	Pyrimidine or purine	Copper Reagent[a]	Lithium amide	Product	Yield (%)[b]
1	 **4a**	 **5a**[c]	LiHMDS **6b**	 **7b**	81
2	**4a**	**5a**[c]	 **6c**	 **7c**	76
3	 **4b**	 **5b**[d]	 **6a**	 **8b**	69
4	**4b**	**5b**[d]	TMPLi **6d**	 **7d**	70
5	 **4c**	 **5c**[c]	LiHMDS **6b**	 **7e**	79
6	**4c**	**5c**[c]	 **6e**	 **7f**	68
	 **4d**	 **5d**			
7	**4d**	**5d**[d]	**6a**: X = O	**7g**: X = O	78
8	**4d**	**5d**[d]	**6f**: X = NMe	**7h**: X = NMe	78
9	 **4e**	 **5e**[d]	 **6a**	 **7i**	70
10	 **4f**	 **5f**[d]	 **6f**	 **7j**	66
11	 **4g**	 **5g**[d]	 **6a**	 **7k**	63
12	 **4h**	 **5h**[d]	Et_2NLi **6g**	 **7l**	66
13	 **4i**	 **5i**[d]	 **6a**	 **7m**	69
14	 **4j**	 **5j**[d]	**6f**	**7n**	70

[a] Organocopper reagent of type **5** were obtained after transmetalation of the corresponding organomagnesium reagent using CuCl·2LiCl. [b] Isolated yield of analytically pure product. [c] 1.2 equiv of $(Et_2NCH_2CH_2)_2O$ was added. [d] 1.2 equiv of Et_3N was added.

Scheme 2. Amination at C6 Position of the Iodopurine **4k**: Application of to the Synthesis of Adenine Derivative (**7o**) and Purvalanol A (**3**)



(Scheme 2),[19] followed by a Cu(I)-transmetalation, the cuprated purine **5k** was obtained. An oxidative amination on **5k** with LiHMDS (**6b**) provided the protected adenine **7o** in 76% yield after a desilylation using TBAF (Scheme 2). We have applied the new amination procedure to the synthesis of the CDK inhibitor, purvalanol A (**3**). Thus, the amination of the 6-cuprated purine **5k** with the lithiation N-TBS-aniline derivative (**6h**) gave the expected adenine derivative **7p** in 71% yield. We have completed the synthesis by the reaction of **7p** in a sealed tube with D-valinol in the presence of *Hunig*'s base in *n*-butanol (150 °C, 2 h) affording purvalanol A (**3**) in 65% yield (Scheme 2).

In summary, we have disclosed via new regioselective cuprations a new mild amination procedure of various functionalized cuprated pyrimidines and purines leading to valuable uracil, thymine and adenine derivatives. These aminations[20] proceeded under mild conditions and have a high potential for preparing DNA and RNA nucleoside aminated analogs.

Acknowledgment. We thank the Fonds der Chemischen Industrie and the DFG (SFB 749) for financial support. We thank Chemetall GmbH (Frankfurt), Evonik GmBH (Hanau), and BASF AG (Ludwigshafen) for the generous gift of chemicals. S.R.D. and N.B. thank the Alexander von Humboldt Foundation and Sanofi-Aventis for fellowships.

Supporting Information Available: Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800353S

(19) This compound was prepared from 2-chloro-6-iodo-9*H*-purine using the Mitsonobu reaction procedure described in the following reference: Toyota, N.; Katagari, A.; Kanebo, C *Synth. Commun.* **1993**, *23*, 1295.

(20) **Typical Procedure. Synthesis of 4-(2,6-Dimethoxypyrimidin-4-yl)morpholine (7a).** A dry and argon-flushed 50 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 2,4-dimethoxypyrimidine (**4a**; 280 mg, 2 mmol, 1 equiv) in dry THF (1 mL). After the mixture was cooled to −40 °C, TMPMgCl·LiCl (1.20 M in THF; 1.84 mL, 1.1 mmol) was added dropwise and stirred for 12 h at −40 °C. The resulting Grignard reagent was then added dropwise to a solution of CuCl·2LiCl (1.0 M in THF; 2.4 mL, 2.4 mmol, 1.2 equiv) and bis[2-(*N*,*N*-dimethylamino)ethyl] ether (284 mg, 2.4 mmol, 1.2 equiv) at −50 °C and was stirred for 45 min affording the corresponding copper reagent **5a**. *N*-Lithium morpholide (**6a**; 4 mmol) was added dropwise and the mixture was further stirred for 1 h at −60 °C. The reaction mixture was cooled to −78 °C, then chloranil (590 mg, 2.4 mmol) in dry THF (14 mL), was slowly added over a period of 1 h. The reaction mixture was stirred for 12 h at this temperature. Ether (20 mL) was added to the crude reaction mixture, it was filtered through Celite, and washed with ether (100 mL). The organic phase was washed with 2 × 20 mL portions of a 2 M aq NH_4OH solution and extracted with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography (SiO_2, pentane/ether; 4:1) affording the aminated pyrimidine **7a** (341 mg, 76%) as a gray solid (mp 93.9–95.7 °C).