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Chemo- and Regioselective Functionalization of Uracil Derivatives. Applications to the Synthesis of Oxypurinol and Emivirine

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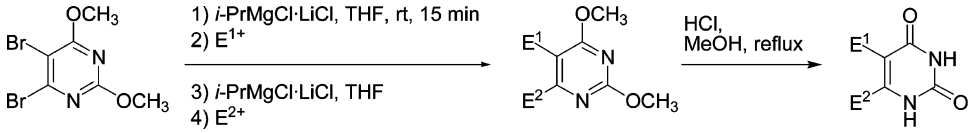
ABSTRACT



A novel route for the synthesis of 4,5-difunctionalized uracils using a chemo- and regioselective bromine/magnesium exchange reaction on 5-bromo-4-halogeno-2,6-dimethoxypyrimidines has been developed. Applications to the synthesis of pharmaceuticals such as oxypurinol and emivirine are reported.

The preparation of functionalized uracil derivatives is of interest because the uracil unit is present in DNA and related natural products, such as the marine alkaloid rigidin **1** (Figure 1).[1]Uracils are privileged structures in drug discovery[2] and

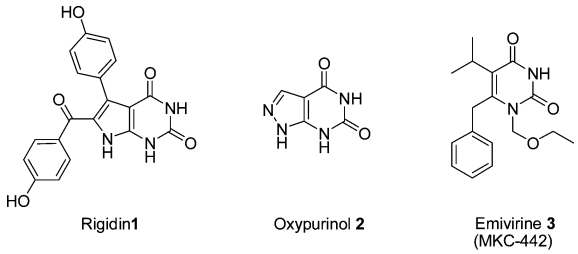


Figure 1. Uracil derivatives.

display a broad spectrum of biological activities. For example, 5-fluorouracil[3] is an important anticancer agent widely used in oncology. Oxypurinol **2**[4] is a xanthine oxidase inhibitor, which is the active metabolite of the drug allopurinol. In recent years, several pathways for the synthesis of analogues from emivirine **3**,[5] belonging to a nonnucleoside[5b] class (NNRTIs) of inhibitors that target the retrovirus HIV-1, were developed. The functionalizations of uracil derivatives at the C4 or C5 position are therefore of great synthetic importance. Generally, these functionalizations require the protection of the carbonyl groups, and the introduction of functionality is implemented by directed lithiation[6] or bromine−lithium exchange[7] starting from 5-halogeno-2,6-dialkoxypyrimidines. These methods allow the preparation

(1) (a) Sakamoto, T.; Kondo, Y.; Sato, S.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, *5*, 459. (b) Lagoja, I. M. *Chem. Biodiversity* **2005**, *2*, 1.

(2) Newkome, G. R.; Pandler, W. W. *Contemporary Heterocyclic Chemistry*; Wiley: New York, 1982.

(3) Cai, T. B.; Tang, X.; Nagorski, J.; Brauschweiger, P. G.; Wang, P. G. *Bioorg. Med. Chem.* **2003**, *11*, 4971.

(4) Nagamatsu, T.; Fujita, T.; Endo, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 33. Allopurinol is a well-known drug clinically used for the treatment of gout and hyperuricemia. Oxypurinol is currently being developed by Cardiome Pharma for the treatment of allopurinol-intolerant hyperuricemia (gout) and is in phase III trials for the treatment of congestive heart failure.

(5) (a) Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Inouye, N.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1995**, *38*, 2860. (b) Pedersen, O. S.; Pedersen, E. B. *Antiviral Chem. Chemother.* **1999**, *10*, 2860.

(6) (a) Schinazi, R. F.; Prusoff, W. H. *J. Org. Chem.* **1985**, *50*, 841. (b) Chan, S. A.; Chen, G.; Guo, R.; Wu, J. PCT Int. Appl. 2005, 2005108377.

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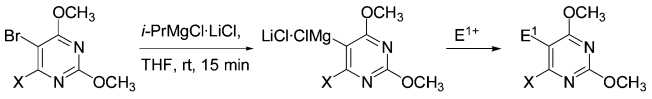
of various uracil derivatives, but they require low temperatures and preclude the presence of sensitive functional groups. The magnesiation of 5-bromo-2,6-dialkoxypyrimidines has also been described.[8,9]

Recently, we have found a LiCl-catalyzed Br/Mg exchange[10] reaction using *i*-PrMgCl·LiCl.[11] This reagent considerably accelerates the bromine/magnesium exchange reaction on aryl and heteroaryl bromides. Herein, we wish to report a general preparation of difunctionalized uracil derivatives at the C4 and C5 positions, starting from 5-bromo-4-halogeno-2,6-dimethoxypyrimidines (**4** and **5**). The utility of this method is demonstrated by performing the synthesis of oxypurinol **2** and emivirine **3**.

Thus, the addition of *i*-PrMgCl·LiCl to 5-bromo-4-chloro-2,6-dimethoxypyrimidine[12] (**4**) at 20 °C in THF furnished quantitatively,[13] within 15 min, the magnesiated *N*-heterocycle **6** (Scheme 1, Table 1). This magnesium reagent reacted

Scheme 1. Chemo- and Regioselective Functionalizations of 5-Bromo-4-halogeno-2,6-dimethoxypyrimidines at the C5 Position



4: X= Cl
5: X= Br

6: X= Cl
7: X= Br

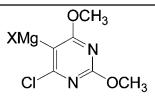
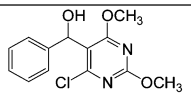
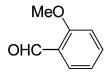
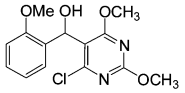
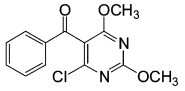
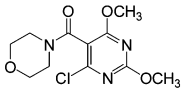
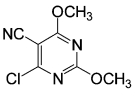
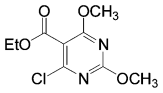
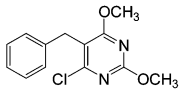
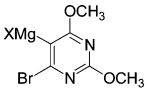
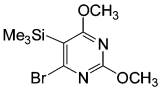
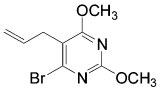
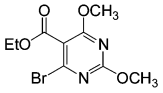
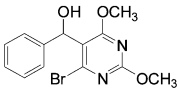
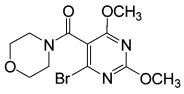
8: X= Cl
9: X= Br

with a wide range of electrophiles providing new 5-functionalized 4-chloro-2,6-dimethoxypyrimidines of type **8a**−**g** in high yields, after quenching with an electrophile (Scheme 1, Table 1, entries 1−7).

Addition of benzaldehyde or 2-methoxybenzaldehyde on metalated species **6** led to the corresponding alcohols **8a** and **8b** in, respectively, 91 and 83% yield (entries 1 and 2). The reaction with acid chlorides such as PhCOCl or a carbamoyl chloride provided the ketone **8c** in 86% yield and the amide **8d** in 85% yield (entries 3 and 4). Treatment of the magnesiated derivative **6** with TsCN afforded the heterocyclic nitrile **8e** in 89% yield (entry 5). The introduction of an ester group was best performed by the reaction with NC−CO_2Et leading to the ester **8f** in 87% yield (entry 6). The reaction with an activated bromide, such as benzyl bromide, provided the expected product **8g** in 75% yield (entry 7).

Similarly, starting from 4,5-dibromo-2,6-dimethoxypyrimidine[14] (**5**), the Br/Mg exchange reaction occurred regio-

Table 1. Products of Type **8** and **9**

entry	Grignard reagent[a]	electrophile	product of type **8** and **9**	yield (%)[b]
1	 **6**	PhCHO	 **8a**	91
2	**6**		 **8b**	83
3	**6**	PhCOCl	 **8c**	86
4	**6**		 **8d**	85
5	**6**	TsCN	 **8e**	89
6	**6**	$NCCO_2Et$	 **8f**	87
7	**6**	$PhCH_2Br$	 **8g**	75
8	 **7**	TMSCl	 **9a**	91
9	**7**	allyl bromide	 **9b**	91
10	**7**	$NCCO_2Et$	 **9c**	81
11	**7**	PhCHO	 **9d**	95
12	**7**		 **9e**	70

[a] X = Cl·LiCl. [b] Isolated yield of analytically pure product.

selectively at C5, providing the corresponding magnesium species **7** (Scheme 1, Table 1). The reaction of the Grignard reagent intermediate **7** with various electrophiles gave the

(7) (a) De Corte, B. L.; Kinney, W. A.; Liu, L.; Ghosh, S.; Brunner, L.; Hoekstra, W. J.; Santulli, R. J.; Tuman, R. W.; Baker, J.; Burns, C.; Proost, J. C.; Tounge, B. A.; Damiano, B. P.; Maryanoff, B. E.; Johnson, D. L.; Galemmo, R. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5227. (b) Reese, C. B.; Wu, Q. *Org. Biomol. Chem.* **2003**, *1*, 3160.

(8) Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Masataka, Y. *J. Org. Chem.* **1998**, *63*, 7207.

(9) Shimura, A.; Momotake, A.; Togo, H.; Yokoyama, M. *Synthesis* **1999**, 495.

(10) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.

(11) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

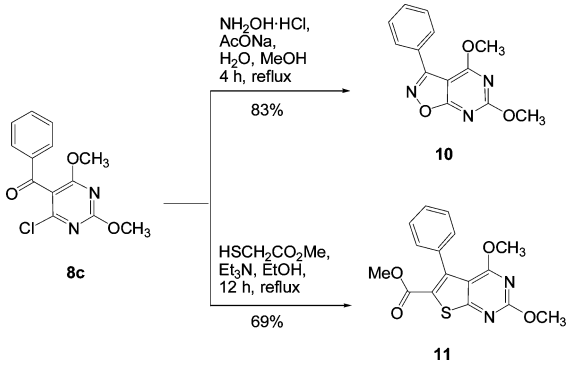
(12) Okafor, C. *J. Org. Chem.* **1973**, *38*, 4386.

(13) The completion of the Br−Mg exchange was checked by GC analysis of reaction aliquots quenched with saturated NH_4Cl (aqueous).

expected products **9a**−**e** in very high yields (Scheme 1, Table 1, entries 8−12). The silylation and the direct allylation of the magnesium derivative **7** can be accomplished, respectively, with TMSCl and allyl bromide, leading to pyrimidines **9a** and **9b** with 91% yield (entries 8 and 9). Trapping the magnesium species **7** with ethyl cyanoformate, benzaldehyde, or 4-morpholinecarbonyl chloride furnished the highly corresponding functionalized products **9c**−**e** in 70−95% yields (entries 10−12).

The pyrimidines of type **8** can be converted into various annelated heterocycles. Thus, the reaction between the chloroketone **8c** and the hydroxylamine hydrochloride in a 1:1 mixture of H_2O/MeOH gave, within 4 h, the desired product **10** in 83% yield (Scheme 2). Interestingly, the

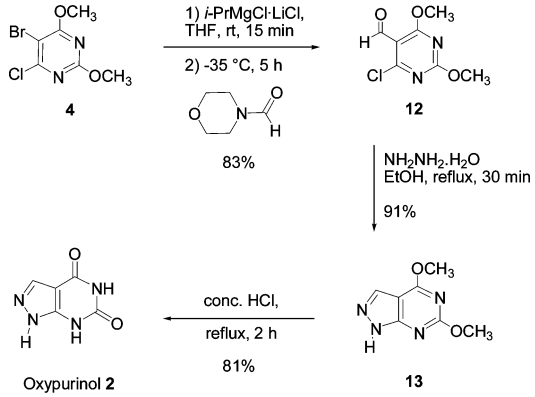
Scheme 2. Synthesis of Annelated Heterocycles



addition of methyl mercaptoacetate on **8c**, in the presence of triethylamine,[15] provided the bicyclic *S*,*N*-heterocycle **11** in 69% yield (Scheme 2).

As an application, we also used an intramolecular cyclization to prepare the drug oxypurinol **2** (Scheme 3). Thus, the

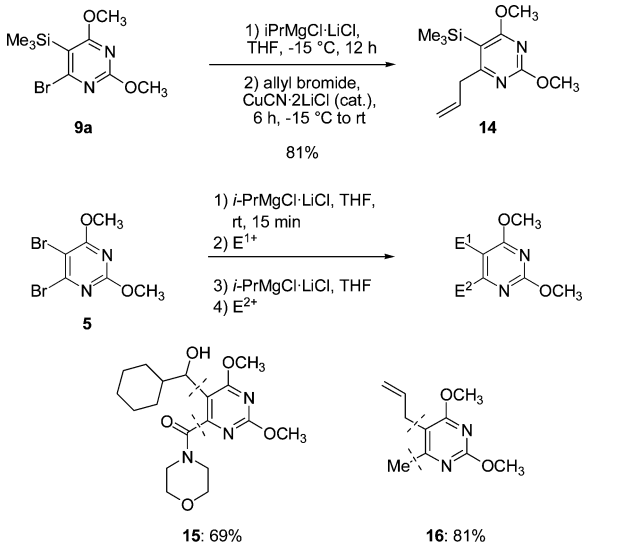
Scheme 3. Synthesis of Oxypurinol **2**



reaction of pyrimidine **4** with *i*-PrMgCl·LiCl (1.05 equiv, rt, 15 min) followed by the reaction with *N*-formylmorpholine provided the aldehyde **12** in 83% yield. Treatment of **12** with an excess of hydrazine monohydrate[16] led to the bicyclic *N*-heterocycle **13** in 91% yield (80 °C, 0.5 h). Deprotection using concentrated HCl led to oxypurinol **2** in 81% yield (Scheme 3).

A successive introduction of two different electrophiles in positions C4 and C5 can be performed. Thus, the reaction of 4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (**9a**) with *i*-PrMgCl·LiCl at −15 °C for 12 h furnished the corresponding Grignard reagent which could be trapped with allyl bromide and gave the expected product **14** in 81% yield (Scheme 4).

Scheme 4. Difunctionalizations of 4,5-Dibromo-2,6-dimethoxypyrimidine via Successive One-Pot Br/Mg Exchange Reactions



Interestingly, difunctionalizations with two successive Br/Mg exchange reactions using a "one-pot" procedure could also be performed. Thus, by using successively *c*-HexCHO and *N*-morpholinecarbonyl chloride as electrophiles, we obtained the desired product **15** in 69% overall yield. Similarly, by using allyl bromide and MeI, we prepared the 4,5-disubstituted pyrimidine **16** in 81% yield (Scheme 4). To illustrate the versatility of this method, a synthesis of emivirine **3** was performed (Scheme 5). Treatment of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) with *i*-PrMgCl·LiCl followed by the reaction with acetone in the presence of a solution of $LaCl_3$·2LiCl in THF[17] led to the corresponding alcohol **17** in 87% yield. This compound was dehydroxylated using triethylsilane with trifluoroacetic acid.[18] A mixture of the expected 4-bromo-5-isopropyl-2,6-dimethoxypyrimidine (**18**) and the corresponding dehydrated product was ob-

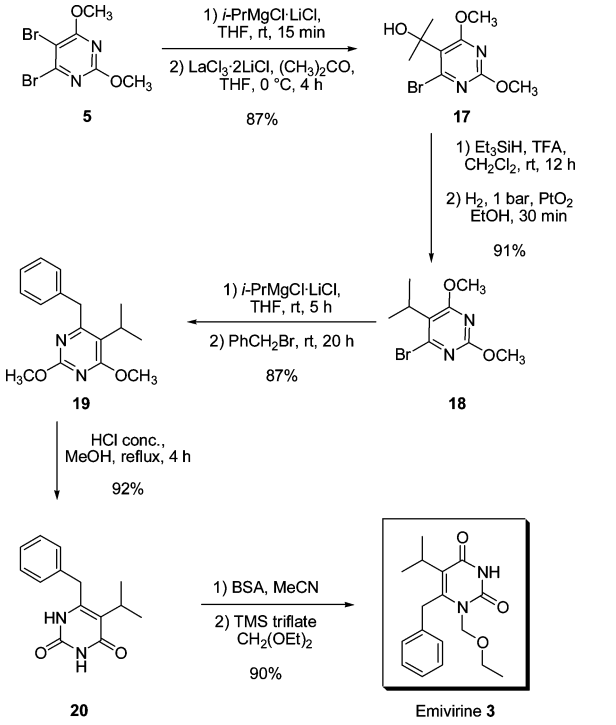
(14) For the preparation of 4-bromo-2,6-dimethoxypyrimidine: White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963.

(15) Rahman, L. K. A.; Scrowston, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, *3*, 385.

(16) Nagamatsu, T.; Fujita, T.; Endo, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 33.

(17) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.

Scheme 5. Synthesis of Emivirine **3**



tained.[19] The product mixture was directly hydrogenated using PtO_2 [20] (1 bar, 30 min), and we obtained **18** in 91% yield.

The second Br/Mg exchange was performed at room temperature for 5 h, followed by the benzyl bromide addition, leading to the 4,5-dialkylated-2,6-dimethoxypyrimidine species (**19**) (20 h, rt, 87% yield). An acidic hydrolysis in aqueous MeOH gave the corresponding uracil **20** in 92% yield after recrystallization from aqueous MeOH. Compound **20** was preliminarily silylated using BSA in MeCN and then N-alkylated[21] with diethoxymethane to furnish 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (**3**, emivirine) in 90% yield (Scheme 5).

In summary, we have developed a selective functionalization method[22] of uracils in the C4 and C5 positions via successive Br/Mg exchanges allowing the synthesis of various new polyfunctionalized uracils. We have applied this method to the synthesis of biologically active uracils, such as oxypurinol and emivirine, and opened a new route to the synthesis of their analogues.

Acknowledgment. We thank the Fonds der Chemischen Industrie for financial support and Sanofi-Aventis for a fellowship to N.B.

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.

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(18) Albert, J. S.; Aharony, D.; Andisik, D.; Barthlow, H.; Bernstein, P. R.; Bialecki, R. A.; Dedinas, R.; Dembofsky, B. T.; Hill, D.; Kirkland, K.; Koether, G. M.; Kosmider, B. J.; Ohnmacht, C.; Palmer, W.; Potts, W.; Rumsey, W.; Shen, L.; Shenvi, A.; Sherwood, S.; Warwick, P. J.; Russell, K. *J. Med. Chem.* **2002**, *45*, 3972.

(19) A mixture of 17% of **18** and 83% of the corresponding dehydrated product was obtained by ^{1}H NMR analysis of the crude product.

(20) Tilley, J. W.; LeMahieu, R. A.; Carson, M.; Kierstead, R. W. *J. Med. Chem.* **1980**, *23*, 92.

(21) Therkelsen, F. D.; Hansen, A.-L. L.; Pedersen, E. B.; Nielsen, C. *Org. Biomol. Chem.* **2003**, *1*, 2908.

(22) (a) **Procedure for the Br/Mg exchange reaction at C5 (synthesis of 9a):** A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4,5-dibromo-2,6-dimethoxypyrimidine (**5**) (596 mg, 2 mmol) in dry THF (3 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 2.1 mmol, 1.05 equiv) was added slowly (within 5 min) at room temperature, and the resulting mixture was stirred for 15 min to complete the bromine−magnesium exchange (checked by GC-MS analysis of reaction aliquots). Trimethylsilyl chloride (240 mg, 2.2 mmol, 1.1 equiv) was added dropwise. The mixture was stirred at room temperature for 24 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic fractions were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 4:1) yielded 529 mg (91% yield) of **9a** as a white solid (mp: 71.1−72.2 °C). (b) **Procedure for the Br/Mg exchange reaction at C4 (synthesis of 14):** A dry and argon-flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 4-bromo-2,6-dimethoxy-5-(trimethylsilyl)pyrimidine (**9a**) (291 mg, 1.0 mmol) in dry THF (2 mL). *i*-PrMgCl·LiCl (1.0 M/THF, 1.05 mmol, 1.05 equiv) was added very slowly at −15 °C, and the resulting mixture was stirred for 12 h at this temperature to complete the bromine−magnesium exchange (checked by GC-MS analysis of reaction aliquots). Then, allyl bromide (145 mg, 1.2 mmol, 1.2 equiv) was added dropwise. After 30 min, 3 drops of CuCN·2LiCl (cat., 1 M in THF) were added. The mixture was warmed at room temperature for 6 h and was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl acetate (3 × 5 mL). The organic fractions were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (*n*-pentane/diethyl ether = 3:2) yielded 204 mg (81% yield) of **14** as a colorless oil.