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Synthesis of 2,4-Disubstituted Pyrimidin-5-yl *C*-2′-Deoxyribonucleosides by Sequential Regioselective Reactions of 2,4-Dichloropyrimidine Nucleosides

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A new modular synthesis of diverse 2,4-disubstituted pyrimidin-5-yl *C*-2′-deoxyribonucleosides by sequential regioselective reactions of 2,6-dichloropyrimidin-5-yl C-nucleosides was developed. The intermediate was prepared by the Heck coupling of 2,6-dichloro-5-iodopyrimidine with glycal followed by desilylation and reduction. Its mild nucleophilic substitutions or Fe-catalyzed cross-coupling with MeMgCl proceeded regioselectively at position 4, whereas at elevated temperatures or with excess of MeMgCl, double substitution occurred. The 2-chloro-4-substituted intermediates undergo another substitution or coupling to afford 2,4-disubstituted derivatives.

Introduction

C-Nucleosides are an important class of molecules which display biological activities and find applications in chemical biology.[1] (Het)aryl *C*-2′-deoxyribonucleosides have attracted prominent attention as candidates for novel base-pairs in the quest for extension of the genetic alphabet.[2] They form stable and selective (usually hydrophobic pairs) in DNA duplexes due to increased packing and hydrophobic interactions.[3] Some artificial base-pairs were efficiently and selectively replicated by DNA polymerases.[4] The most successful pairs based on 4-substituted 2-methoxyphenyl C-nucleosides in combination with thioisocarbostyril base were not only replicated and extended[5] but also used in the first successful PCR with a 6-letter genetic alphabet.[6] Particularly important is the presence of a methoxy group as an H-bond acceptor in the minor groove, which stabilizes the active site of the polymerase and facilitates the extension of the growing DNA chain.

There are numerous approaches[1,7] to the synthesis of C-nucleosides, but none of them is general, and some suffer from low efficiency and stereoselectivity. In recent years we have developed[8] a modular approach based on the synthesis of halo(het)aryl C-nucleoside intermediates and their follow-up functionalizations by cross-couplings, aminations and other reactions to afford series (one-dimensional libraries) of derivatives. Since it is known that many dihaloheterocycles undergo regioselective or chemoselective cross-couplings[9] or nucleophilic substitutions, we decided to extend our approach to the synthesis of hetaryl C-nucleosides bearing two different substituents (two-dimensional libraries) by sequential double substitutions of dihalohetaryl intermediates. Here we report on the first example of this approach for the synthesis of 2,4-disubstituted-pyrimidin-5-yl C-nucleosides.[10]

Results and Discussion

The synthesis of the key intermediate was based on the Heck reaction[11] of 3′-TBDMS-protected glycal **1** with 2,4-dichloro-5-iodopyrimidine **2** in the presence of $Pd(OAc)_2$, $(PhF_5)_3P$ and Ag_2CO_3, which resulted in the formation of the 2,4-dichloropyrimidin-5-yl nucleoside analogue **3** as a pure β-anomer (no α-anomer formation was observed) (Scheme 1). Since partial desilylation (10–20%) was observed during the reaction and workup, the intermediate **3** was then (without purification) directly deprotected by $Et_3N{\cdot}3HF$ in THF to give ketone **4** in 42% overall yield (from **1**). Subsequent reduction of **4** by triacetoxyborohydride in a mixture of acetonitrile/acetic acid gave the key intermediate, 2,4-dichloropyrimidin-5-yl C-nucleoside **5** in 80% yield as a pure β-anomer. Its crystal structure was determined by X-ray diffraction (Scheme 1) to show interesting Cl····N bonds[12] of the chlorine atom at position 4 to N3 of the neighbouring pyrimidine ring in the crystal (see Supporting Information). Its silylation afforded TBDMS-protected C-nucleoside **6** in 75% yield.

The dichloropyrimidine intermediate **5** was then subjected to a series of nucleophilic substitutions (Scheme 2, Table 1). The reaction with methanolic ammonia at room temp. gave regioselectively 4-amino-2-chloro derivative **7** in 74% yield. Similarly, the treatment with sodium methoxide in methanol gave regioselectively 2-chloro-4-methoxy derivative **8** in 78% yield. The regioselectivity was verified by

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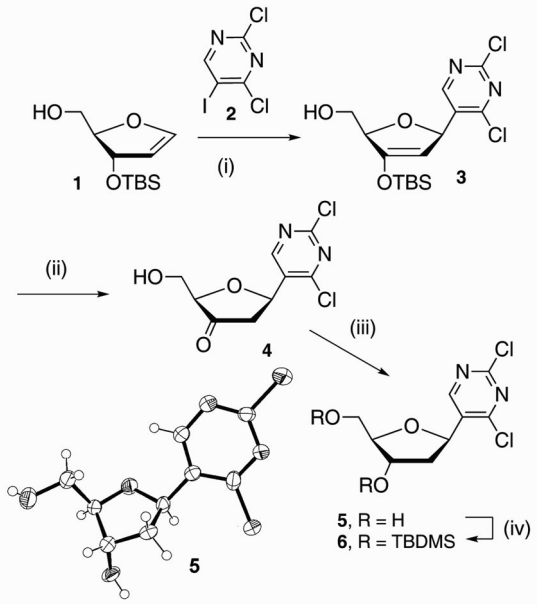
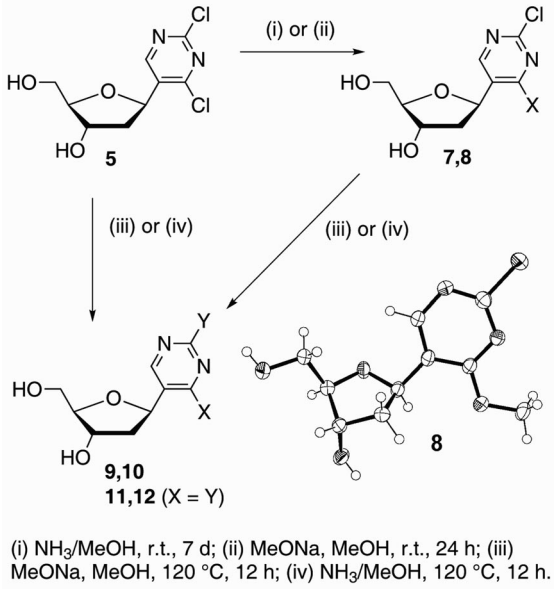


Scheme 1. Synthesis of 2,4-dichloropyrimidin-5-yl C-nucleoside intermediates.



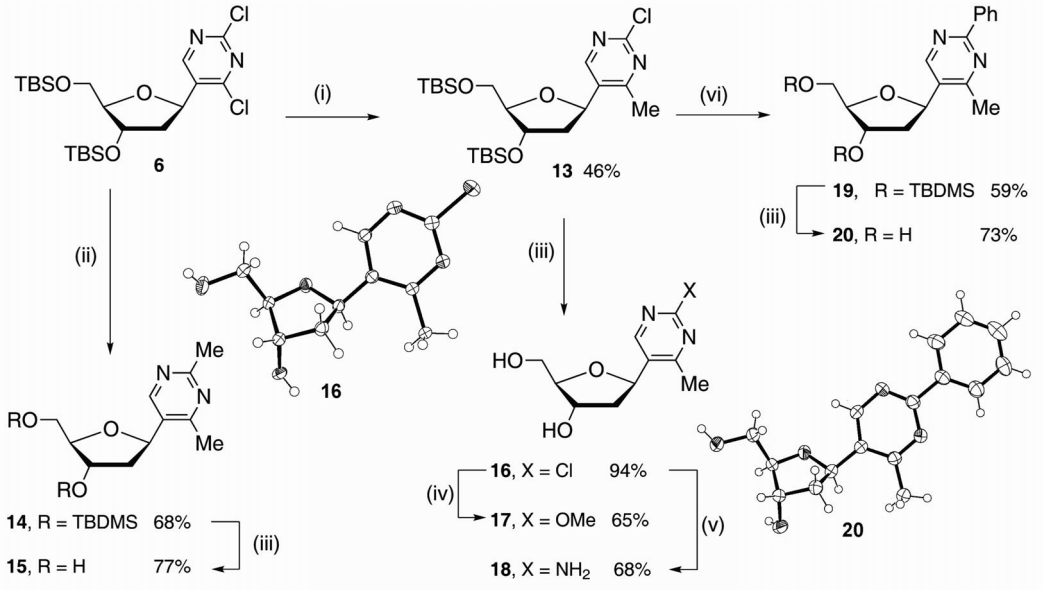
Scheme 2. Regioselective nucleophilic substitutions.

X-ray diffraction of compound **8** (Scheme 2). The second chlorine atom can be still replaced by another substitution. Thus, 4-amino-2-chloro derivative **7** was converted to 4-amino-2-methoxypyrimidine **9** by heating with sodium methoxide in methanol in 71% yield. However, when we attempted the amination of 2-chloro-4-methoxy derivative **8** with methanolic ammonia at 120 °C, a mixture of three

Table 1. Regioselective nucleophilic substitutions.

Entry	Starting compound	Conditions	X	Y	Product (yield)
1	**5**	i	NH_2	–	**7** (74%)
2	**5**	ii	OMe	–	**8** (78%)
3	**7**	iii	NH_2	OMe	**9** (71%)
4	**8**	iv	OMe	NH_2	**10** (25%)[a]
5	**5**	iv	NH_2	NH_2	**11** (83%)
6	**5**	iii	OMe	OMe	**12** (87%)

[a] Accompanied by **7** (52%) and **9** (15%).



Scheme 3. Cross couplings and follow-up substitutions of TBDMS-protected nucleoside **6**.

products was obtained. The desired 2-amino-4-methoxypyrimidine **10** was isolated in 25% yield, accompanied by 4-amino-2-chloro derivative **7** (52%) and 4-amino-2-methoxypyrimidine **9** (15%). Apparently, under these harsh conditions, the 4-OMe substituent acts as a leaving group, which can be replaced by an amino group, and methanol may serve as a nucleophile to methoxylate the C-2 position by replacing the chlorine atom. On the other hand, the reaction of **5** with methanolic ammonia at 120 °C gave cleanly the 2,4-diamino derivative **11** as product of disubstitution in 83% yield. Also, the reaction with excess of sodium methoxide under heating gave disubstituted 2,4-dimethoxy derivative **12** in 87% yield.

Silylated C-nucleoside **6** was subjected to Fe-catalyzed cross-coupling[13,14] with MeMgCl in the presence of $Fe(acac)_3$ (Scheme 3). When using 1.5 equiv. of MeMgCl, monosubstituted 2-chloro-4-methyl derivative **13** was regioselectively prepared in 46% yield, whereas the use of 4 equiv. of MeMgCl gave 2,4-dimethyl derivative **14** in 68% yield. The silylated derivatives **13** and **14** were readily deprotected by treatment with $Et_3N{\cdot}3HF$ to give the free nucleosides **15** and **16**. The free 2-chloro-4-methylpyrimidine nucleoside **16** was then subjected to nucleophilic substitutions with NaOMe or methanolic ammonia at 120 °C giving rise to 2-methoxy- or 2-amino-4-methylpyrimidines **17** and **18** in 65 and 68%, respectively. The Suzuki cross-coupling of silylated intermediate **13** with $PhB(OH)_2$ in the presence of $Pd(PPh_3)_4$ gave 2-phenyl-4-methylpyrimidine nucleoside **19** in 59% yield, which was further desilylated by using $Et_3N{\cdot}3HF$ to give the free C-nucleosides **20** in 73% yield. The regioselectivity of the substitutions was independently confirmed by NMR spectroscopy for all compounds and by X-ray crystal structure analysis of the free C-nucleosides **16** and **20**.[15]

Conclusions

Unprotected or protected 2,4-dichloropyrimidin-5-yl C-2′-deoxyribonucleosides **5** and **6** are excellent intermediates for regioselective sequential double substitutions leading to pyrimidine C-nucleosides bearing two different substituents in positions 2 and 4. The chlorine atom at position 4 is significantly more reactive in nucleophilic substitutions and cross-couplings than the chlorine atom at position 2. Thus, nucleophilic substitutions under mild conditions (room temp.) proceed regioselectively at position 4 to give 4-substituted 2-chloropyrimidine derivatives that readily undergo another substitution at elevated temperature (120 °C). The same reactions at 120 °C lead to 2,4-disubstituted products. Fe-catalyzed cross-coupling of silylated intermediate **6** with 1.5 equiv. of MeMgCl gives regioselectively 2-chloro-4-methylpyrimidinyl nucleoside **13**, whereas the reaction with 4 equiv. of the Grignard reagent affords 2,4-dimethylpyrimidine **14**. The 4-chloro-2-methyl intermediate **13** or its desilylated derivative **16** can be used for another cross-coupling or nucleophilic substitution to prepare a series of 2-substituted 4-methylpyrimidine nucleosides. The only nonselective reaction was the amination of 2-chloro-4-methoxypyrimidine **8** at high temperature when the OMe group was also partially replaced.

This methodology is a general approach to the synthesis of diverse 2,4-disubstituted pyrimidine C-nucleosides by the sequential reactions with two different nucleophiles (the first one at position 4 and the second one at position 2). It can be used in the synthesis of important pyrimidine nucleosides with different substituents pointing to the minor and major groove of DNA. In this respect, the 4-methoxypyrimidine nucleosides **8**, **10** and **12** seem to be promising candidates for new efficiently replicable base-pairs.[6] Moreover, this approach is applicable in the synthesis of a 2D library of derivatives. Studies along these lines are now in progress in our laboratory.

Supporting Information (see footnote on the first page of this article): Complete Experimental Section and additional figures of crystal structures and packings.

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[15] CCDC-754783 (for **5**), -754784 (for **8**), -754785 (for **16**), -754786 (for **20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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