A New Modular and Practical Methodology for the Synthesis of 4- or 3-Substituted Phenyl C-Nucleosides

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A novel efficient and practical approach to the synthesis of 4- or 3-substituted phenyl C-nucleosides has been developed. It consists in coupling of protected halogenose **1** with bromophenylmagnesium bromides followed by acid mediated epimerization to prepare 4- or 3-bromophenyl C-nucleoside intermediates. Their Pd-catalyzed cross-coupling reactions with diverse organometallics followed by deprotection afforded the title nucleoside analogues.

Introduction

C-Nucleosides are an important class of compounds characterized by replacement of labile nucleosidic C–N bond by a stable hardly degradable C–C bond. Many of them possess antiviral or antineoplastic activities.[1] Quite recently, C-nucleosides bearing simple hydrophobic aryl and hetaryl groups as nucleobase surrogates attracted great attention due to their use in the extension of the genetic alphabet.[2] If incorporated to oligonucleotides, they selectively pair with the same of other hydrophobic nucleobase to form stable duplexes due to increased stacking and favourable desolvation energy as compared to canonical nucleobases.[3] Among C-nucleosides, biaryl nucleobase analogues are of particular interest due to the pronounced stacking interactions.[4] Biaryl or even oligoaryl C-nucleosides have also been used as fluorophoric probes.[5]

There is a number of synthetic approaches to C-nucleosides.[6] The most general methodologies are (i) additions of organometallics to ribono- or 2-deoxyribonolactones[4,7] or (ii) coupling of a halogenose with organometallics.[8,9] The latter approach using diaryl cadmium reagents[5,8] is the most commonly used method for aryl and biaryl C-nucleosides. It consists in construction of a suitable aryl bromide, its conversion to Grignard reagent, transmetallation to diarylcadmium and coupling with halogenose. The main coupling product is usually undesired α-anomer that is converted into the β-anomer by acid-catalyzed isomerization. There are several drawbacks of this approach: (i) organocadmium reagents are extremely toxic and environmentally harmful, (ii) one equivalent of the aryl group from diarylcadmium is lost, (iii) conditions for coupling and isomerization must be optimized for each derivative and (iv) the method is not compatible for many functionalized aryl groups.

In this communication we present a novel modular and non-toxic approach to the synthesis of 4-substituted phenyl C-nucleosides based on a facile synthesis of protected 4- or 3-bromophenyl C-nucleoside intermediates and their standard cross-coupling reactions[10] with diverse organometallics.

Results and Discussion

The key starting compound is the bis-toluoyl protected halogenose **1**[11] very easily available in three steps from 2-deoxyribose. First we have tried its coupling with commercially available 4-bromophenylzinc bromide (Scheme 1, Table 1, Entry 1). The reaction gave rather low conversion and the required β-anomer **2** was isolated in nearly negligible yield while the α-anomer **3** in low yield of 15%. Then we have tried an influence of CuI as additive in order to facilitate the reaction by transmetallation to organocuprate but the yields were only slightly improved (Table 1, Entry 2). Then we have tried to directly use 4-bromophenylmagnesium bromide and, to our surprise, this turned out to be the best reagent that gave the desired compound **2** in 12% and its anomer **3** in 39% yields (Table 1, Entry 3). These yields are comparable to the published procedures with the toxic diarylcadmium species.

The next step was to epimerize the undesired α-anomer **3** to the β-anomer **2**. The use of the most common literature procedure[8,9] based on refluxing of the compound in xylene in presence of an arenesulfonic acid and traces of water was in this particular case very sluggish giving a negligible conversion after 48 h. On the other hand, when a mixture of benzenesulfonic acid (BSA) and trifluoroacetic acid (TFA)

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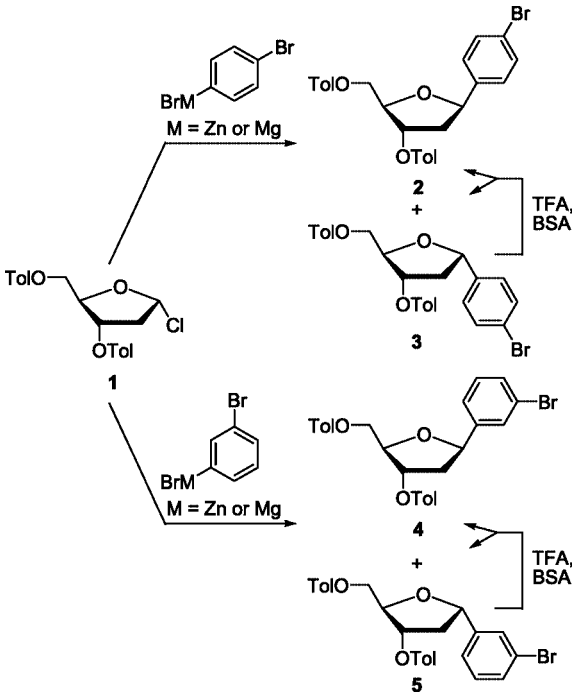


Scheme 1. Syntheses of bromophenyl C-nucleosides.

Table 1. Syntheses of bromophenyl C-nucleosides.

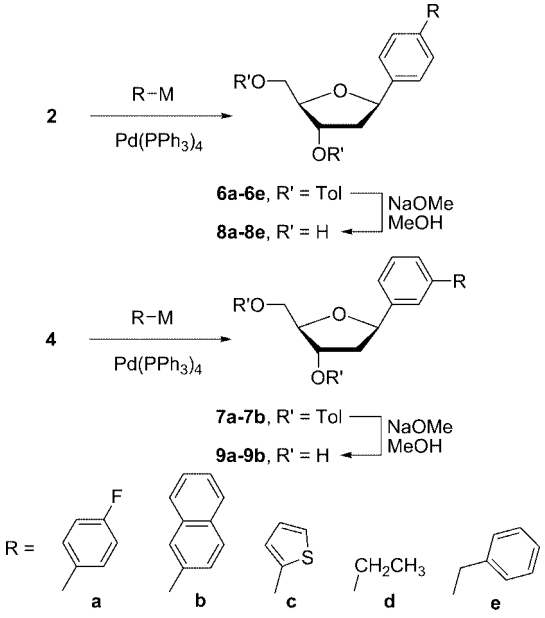
Entry	Starting compd.	Reagent	Additive	β-Anomer (yield)	α-Anomer (yield)
1	**1**	4-BrC_6H_4–ZnBr	none	**2** (2%)	**3** (15%)
2	**1**	4-BrC_6H_4–ZnBr	CuI	**2** (4%)	**3** (18%)
3	**1**	4-BrC_6H_4–MgBr	none	**2** (12%)	**3** (39%)
4	**3**	TFA/BSA	none	**2** (56%)[a]	**3** (22%)
5	**1**	3-BrC_6H_4–ZnBr	none	**4** (3%)	**5** (14%)
6	**1**	3-BrC_6H_4–MgBr	none	**4** (12%)	**5** (31%)
7	**5**	TFA/BSA	none	**4** (3%)	**5** (80%)
8	**5**	TFA/BSA	H_2SO_4	**4** (32%)[b]	**5** (42%)

[a] Preparative yield of **2** was 71% after three turns of the isomerization of **3** and the combined total yield from halogenose **1** after coupling and three turns of isomerization was 40%. [b] Preparative yield of **4** was 45% after two turns of the isomerization of **5** and the combined total yield from halogenose **1** after coupling and two turns of isomerization was 26%.

was used[12] as reagent in dichloromethane at 40 °C, the reaction proceeded very well reaching the equilibrium within 24 h to give the β-anomer **2** in good yield of 56% followed by another 22% of the starting **3** that was recovered and reused (Table 1, Entry 4). This isomerization was repeated three times (combined yield 71% in three turns) and the total yield of the key starting compound **2** from **1** after the coupling and three rounds of isomerization was 40%.

Analogously, the coupling of **1** with 3-bromophenylzinc bromide gave low yields (Table 1, Entry 5) but the coupling with 3-bromophenylmagnesium bromide (Entry 6) gave reasonably good yields of **4** (12%) and **5** (31%). In this case the isomerization of **5** using BSA/TFA was extremely sluggish giving only very low conversion even after 48 h (Entry 7). Therefore the reaction was modified by addition of H_2SO_4 to enhance the rate and after 10 h it gave the desired β-anomer **4** in 32%. This isomerization was repeated two times (combined yield 45% in two turns) and the total yield of **4** from **1** after the coupling and two rounds of isomerization was lower but still acceptable 26%.

Having the optimized multigram-scale procedures for the synthesis of the bromophenyl nucleosides **2** and **4** in hands, cross-coupling reactions of these compounds with diverse organometallics were studied. Thus the 4-bromophenyl nucleoside **2** was subjected to a series of Pd-catalyzed cross-couplings with 4-fluorophenyl- and 2-naphthylboronic acids (Scheme 2, Table 2, Entries 1,2), 2-(tributylstannyl)thiophene (Entry 3), triethylaluminium (Entry 4) and benzylzinc chloride (Entry 5). All these reactions were performed under standard conditions for each type of reaction without any optimization using standard catalysis of $Pd(PPh_3)_4$. In all cases the desired 4-substituted phenyl nucleosides **6a**–**6e** were obtained in good isolated yields of ca. 70%. Similarly, the Suzuki–Miyaura reactions of the 3-bromophenyl nucleoside **4** with 4-fluorophenyl- and 2-naphthylboronic acids gave the 1,3-linked biaryl nucleosides **7a** and **7b** in good yields. Standard deprotection under Zemplen conditions using NaOMe in methanol gave nucleosides **8a**–**8e** and **9a**–**9b** in good yields. All compounds were



Scheme 2. Cross-coupling and deprotection reactions.

Table 2. Cross-coupling and deprotection reactions.

Entry	Starting compd.	R	M	Cross-coupling product (yield)	Deprotection product (yield)[a]
1	**2**	4-fluorophenyl	$B(OH)_2$	**6a** (67%)	**8a** (87%)
2	**2**	2-naphthyl	$B(OH)_2$	**6b** (71%)	**8b** (81%)
3	**2**	2-thienyl	$SnBu_3$	**6c** (79%)	**8c** (78%)
4	**2**	ethyl	$AlEt_2$	**6d** (74%)	**8d** (95%)
5	**2**	benzyl	ZnCl	**6e** (75%)	**8e** (81%)
6	**4**	4-fluorophenyl	$B(OH)_2$	**7a** (68%)	**9a** (83%)
7	**4**	2-naphthyl	$B(OH)_2$	**7b** (82%)	**9b** (74%)

[a] Preparative yield after crystallization.

fully characterized and molecular structure of **8c** was also determined by X-ray diffraction (Figure).[13]

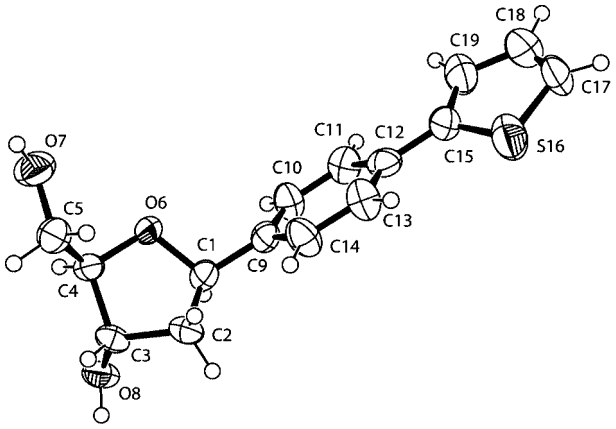


Figure 1. ORTEP drawing of **8c** with the atom numbering scheme. Thermal ellipsoids are drawn at the 50% probability level.

This modular and facile methodology was shown to be a very good alternative to the synthesis of substituted phenyl and biaryl C-nucleosides. It avoids the use of toxic and harmful organocadmium compounds commonly used in the synthesis of this type of nucleosides. There is also no need of optimization of the coupling and isomerization conditions for each arylorganometal reagent. In our methodology, the bromophenylnucleosides are prepared in multigram amounts from very cheap starting compounds (2-deoxyribose and dibromobenzenes) and the subsequent cross-couplings are standard established reactions generally proceeding very well with a variety of commercially available organometallics. As the proof of principle, it was demonstrated on 1,4- and 1,3-dibromobenzene but most likely also other types of dihaloaromatics and heteroaromatics could be in the same way converted to mono-Grignard reagent, coupled with halogenose and eventually used in cross-coupling reaction and thus generate a large series of diverse novel C-nucleosides. Due to its modularity in the choice of the bromoarylmagnesium reagent and organometallic reagent for the cross-coupling, this method could be used even for the construction of libraries of C-nucleosides. Hopefully, it will enable preparation of new types of C-nucleosides for the use in chemical biology and extension of genetic alphabet.

Experimental Section

Coupling of Halogenose 1 with Organomagnesium Reagents: 1,4- or 1,3-Dibromobenzene (4.4 mmol) was added dropwise to magnesium turnings (128 mg, 5.2 mmol) activated by one drop of ethylene bromide in THF (10 mL). The mixture was stirred at 65 °C for 1 h and the resulting solution was added to a solution of **1** (1.2 g, 3 mmol) in THF (50 mL). The mixture was stirred at room temp. for 12 h, poured onto ice containing NH_4Cl, exctracted to ethyl acetate (2 × 100 mL), evaporated, and chromatographed on a silica gel column (hexanes/EA, 10:1) to get products **2** and **3** or **4** and **5**.

Isomerization of α-Anomers: A mixture of BSA (550 mg, 3.5 mmol) and TFA (1.25 mL, 16.8 mmol) was added to a solution of α-anomer **3** or **5** (1 mmol) in dichloromethane (50 mL) (in case of **5**, 1 mL of H_2SO_4 was also added). The mixture was stirred at 40 °C for 24 h and then poured onto ice containing $NaHCO_3$. Products were extracted to chlorophorm and chromatographed as above.

Suzuki–Miyaura Cross-Coupling of 2 or 4: Toluene (15 mL) was added to an argon-purged flask containing bromo derivative **2** or **4** (255 mg, 0.5 mmol), arylboronic acid (1 mmol), K_2CO_3 (100 mg), and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) and the mixture was stirred at 100 °C for 12 h. After filtration and evaporation the mixture was chromatographed as above.

Stille Cross-Coupling of 2: DMF (10 mL) was added to an argon-purged flask containing bromo derivative **2** (255 mg, 0.5 mmol), 2-thienyl(tributyl)stannane (1 mmol), and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) and the mixture was stirred at 100 °C for 12 h. After evaporation, the mixture was chromatographed as above.

Cross-Coupling of 2 with Organozinc or Organoaluminium Reagents: THF (10 mL) was added to an argon-purged flask containing bromo derivative **2** (255 mg, 0.5 mmol), and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) and the mixture was stirred until a clear solution was formed. Then a commercial solution of triethylaluminium or benzylzinc chloride (1 mmol) was added and the mixture was stirred at 70 °C for 12 h. Then it was poured onto ice containing NH_4Cl and EDTA and extracted to ethyl acetate. After evaporation, the mixture was chromatographed as above.

Deprotection of 6 or 7: NaOMe (1 M *solution* in MeOH, 0.1 mL, 0.1 mmol) was added to a solution of **6** or **7** (0.2 mmol) in MeOH (100 mL) and the resulting solution was allowed to stand overnight at room temp. Then it was evaporated and the residue chromatographed on a silica gel column [EA/hexanes (2:1) to EA/MeOH (9:1)]. Products were crystallized from ethyl acetate/heptane.

Supporting Information: Full experimental details and spectral and analytical data for all new compounds (see also the footnote on the first page of this article).

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[13] X-ray crystallographic analysis of single crystal (thin plate, $0.010 \times 0.153 \times 0.365$ mm) was performed with Xcalibur X-ray diffractometer with Cu-K_α (λ = 1.54180 Å), data collected at 295 K. The structure was solved by direct methods with SIR92 [A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435–435] and refined by full-matrix least-squares on F with CRYSTALS [P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, *36*, 1487–1487]. The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. All H atoms were refined with riding constraints. Crystal data: $C_{15}H_{16}O_3S_1$, monoclinic, space group $P2_1$, a = 5.6737(18), b = 9.801(3), c = 12.022(4), β = 100.82(3), V = 656.6(4), Z = 2, M = 276.36, 1873 reflections measured, 1283 independent reflections. Final R = 0.0583, wR = 0.0613 for 781 reflections with $I > 1.96\sigma(I)$ and 173 parameters. CCDC-275179 contains 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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